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Review Article

Quercetin as a promising phytotherapeutic candidate in preeclampsia: a narrative review

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ABSTRACT

Preeclampsia, a pregnancy specific hypertensive disorder, is one of the major cause of maternal and fetal morbidity and mortality globally. It occurs after 20 weeks of gestational period with high blood pressure and proteinuria, primarily caused by abnormal placental development with impaired endothelial function, and widespread inflammation. Current treatment strategies focus on the management of clinical symptoms of this disorder by using pharmaceutical agents like aspirin, Methyldopa, labetalol, hydralazine or nifedipine. But, these drugs cause various adverse effects on pregnancy due to which the researchers have started to explore the potential of several natural bioactive phytoconstituents to discover a safer and healthy alternative. One of these compounds is quercetin, a flavonol that exhibits significant antioxidant, anti-inflammatory, and immune-regulating properties. Preclinical studies have revealed that it helps in maintaining endothelial balance by regulating many inflammatory mediators. Different innovative delivery methods such as nanoparticles and liposomes are being developed to improve its efficacy as a natural therapeutic. The present review will provide insight into the immunology of preeclampsia along with its management by using a multi- targeted and safe natural therapeutic agent i.e. quercetin which in future may be used as an augmented therapy aimed at improving the both maternal and child health.

Keywords: Preeclampsia, Treatment, Management, Quercetin

INTRODUCTION

Preeclampsia (PE) is a pregnancy specific disorder that increases the risk of maternal and neonatal mortality and morbidity. The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines that PE typically manifests after 20 weeks of gestation and is characterized by new-onset hypertension accounting for systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg on two separate occasions at least four hours apart accompanied with proteinuria(≥300 mg/day)/dipstick, or accompanied by systemic complications including renal, hepatic, hematologic, neurological dysfunctions, intrauterine growth restriction or compromised utero-placental perfusion.[1] This disease encircle 2% to 8% of pregnancy-specific complications and responsible for more than 50,000 maternal deaths, and over 500,000 foetal deaths around the globe.[2] Its prevalence is approximately seven times greater in developing countries including India, than in developed regions.[3-5] Pre-existing diseases like diabetes mellitus, chronic hypertension and chronic renal disease along with environmental factors, giving birth either at young or an older age are the crucial risk factors of PE.[6]

The pathophysiology of PE is described as a two-stage process, in which the initial stage is characterized by insufficient trophoblast invasion and abnormal remodeling of the spiral arteries, accompanied by immune alterations within the early maternal–fetal interface. The subsequent stage, occurring later in pregnancy, involves the development of systemic inflammation in the maternal circulation.[7,8] Several studies had suggested that the immune system undergoes significant alterations in PE which is characterized by increased activation of neutrophils, monocytes and lymphocytes, including NK cells, $CD4^+$ T cells, and $CD8^+$ T cells leading to inflammation that disrupts normal pregnancy processes.[9] Under this inflammatory condition, trophoblast undergo necrosis or apo-necrosis. Clearance of this necrotic or apo-necrotic trophoblast by macrophages or dendritic cells leads to the release of pro-inflammatory type-I cytokines such as TNF-α, IL-12, IFN-γ ultimately leading to inadequate placental formation in PE.[7,10]

The current therapeutic management of pre-eclampsia, involves controlling the main symptoms such as managing high blood pressure, preventing seizures, monitoring mother and fetus outcomes, in severe condition the definitive treatment may involve early delivery, sometimes by caesarean section.[11] For the management of maternal blood pressure and eclamptic seizures, antihypertensive and anticonvulsant drugs are being used.[12] Certain NSAIDs such as Aspirin have also shown greater symptom-reducing potential compared with other drug classes but effectiveness of these therapies is strongly influenced by the timing of initiation of the therapy.[13,14] Antenatal corticosteroids are commonly administered to enhance neonatal outcomes, particularly in cases where preterm delivery is anticipated. The use of synthetic drugs during pregnancy is often restricted due to their potential risks to fetal growth and development and concerns about possible teratogenic outcomes.[15] Consequently, exploration of herbal therapeutics and nutraceuticals may prove to be safer and potentially more effective alternatives for PE.[16]

Additionally, dietary phytochemicals, such as natural vitamins and food-derived polyphenols, had evolved considerable during pregnancy.[17] These are a heterogeneous group of more than 8000 different biologically active compounds present in plant-based foods like fruit and beverages (fruit juice, wine, tea, coffee, chocolate, and beer) and, to some lesser extent vegetables, dry legumes and cereals.[18] The major groups of polyphenols include flavonoids, phenolic acids, stilbenes, and lignans. Among these, flavonoids are the most abundant polyphenols in the diet and can be subcategorized as anthocyanins, chalcones, dihydrochalcones, dihydroflavonols, flavonols, flavanones, flavones and bioflavonoids.[19]

Recently, a bioflavonoid named quercetin, is being identified as a potent modulator exhibiting strong antioxidant, vasodilatory and anti-inflammatory activities is gaining much attention in treatment of various ailments.[21] It is found in 20 different species of plants and found in many food products like apples, red grape, kales, cherries, onions, broccoli, berries, edible seeds, tomatoes and tea.[20] Quercetin also manifests antioxidant properties both in vivo and in vitro and its free radical scavenging activity acts as a protective agent against various age-associated disorders. In addition, it is found that the supplements of quercetin exhibit antiviral effects against pathogenesis of virus including virus entry, replication, translation, and protein synthesis. These antiviral activities are demonstrated to be enhanced when it is used in combination with other supplements, such as vitamin C. Various clinical studies suggests that it can also be used as preventive treatment for various chronic diseases such as cardiovascular disorders and pregnancy related disorders like PE.[22] In PE, it may be helpful in restoring the immunological balance by exerting both anti-inflammatory and antihypertensive effects, necessary for managing this disorder. In addition, this compound has been validated for its safety, demonstrating nontoxic effects even with relatively high daily consumption during pregnancy.[23] It had also demonstrated positive effects on embryonic, foetal, and placental development without causing teratogenic or abortifacient effects.[24] Therefore, the use of this compound or its supplements may appear as a potentially safe and effective drug for protection against PE. In the present review, we explore the immunology and the current management strategies of PE with special emphasis on a naturally derived bioactive compounds, quercetin which is a potential supportive and alternative intervention in the management of PE. By integrating existing clinical and preclinical evidence, this review highlights emerging therapeutic avenues and emphasizes quercetin as a novel and promising candidate for improving maternal and foetal outcomes in PE.

IMMUNOLOGY OF PREECLAMPSIA

The immune system of mother plays a crucial role in the development and progression of pregnancy by acting as a protector and effector both.[26] It supports important pregnancy stages like blastocyst implantation, placental development, trophoblast invasion, and remodeling of spiral arteries.[27] The innate immune cells like macrophages, dendritic cells, natural killer (NK) cells, neutrophils, and T cells are up-regulated during pregnancy in order to safeguard the mother against infections while the adaptive immune system is subdued to prevent a targeted immune attack on the developing fetus. Together, innate and adaptive immune system contribute to a finely tuned immunoregulatory mechanism, which is required for maintaining a successful pregnancy.[28]

During normal pregnancy, the human decidua harbors a large population of immune cells, dominated by macrophages, natural killer (NK) cells, and regulatory T (Treg) cells.[25] Among these, NK cells are predominant, accounting for approximately 70–75% of cells, whereas macrophages and dendritic cells account for 20–25% and

1–2%, respectively. The regulatory T cells (Tregs) are essential mediators of tolerance, sustaining immune homeostasis during fertilisation, implantation, and during the entire pregnancy.[29,30] However, an imbalance in the subsets of T helper cells, overactivation of NK cells in the decidua, and increased recruitment of innate immune cells are observed in PE, which collectively lead to the breakdown in immune tolerance creating a pro-inflammatory environment that inhibits the differentiation and expansion of Tregs in PE.[31] Additionally, the maternal-fetal tolerance is supported by many cytokines secreted by helper T cell (Th1 and Th2) for the maintenance of pregnancy and tolerance of the fetus by the maternal immune system.[32] The Th2 cytokines like IL-10, IL-4, IL-5 and IL-13 act as protectors during mid-gestation, while Th1 cytokines like IL-2, TNF-α, IL-1β, and IFN-γ act as effectors during pregnancy. The imbalance in these cytokines can lead to adverse pregnancy outcomes, such as spontaneous abortion, pre-eclampsia and premature birth.[8] Several studies suggested that the pro-inflammatory cytokine, interleukin-6 (IL-6) contributes to immune modulation by suppressing the activity of IL-1 and TNF-α, promoting antibody production by B cells, and enhancing T-cell activation. The elevated serum or plasma levels of IL-16 are being consistently reported in women with PE, highlighting its significant involvement in the disease's pathogenesis.[33] It is also observed that tumor necrosis factor-alpha (TNF-α) is expressed throughout the gestation in placental and uterine tissues at significantly higher concentrations in preeclamptic women, implying its role in the disease development. In addition, the decidual Tregs are reported to be subsequently reduced at the maternal–fetal interface that may impair immune tolerance and result in fetal immunological rejection. Therefore, a balanced innate immune system is essential for the development, maintenance and successful progression of a healthy pregnancy.

THERAPEUTIC MANAGEMENT OF PREECLAMPSIA

The current therapeutic management of PE mainly focuses on the maintenance of mother and fetal health by monitoring them during the entire gestational period. It involves the consistent testing of maternal blood pressure and fetal well-being along with the use of pharmacological drugs. The primary therapeutic options involve the use of antihypertensive medications such as Methyldopa, labetalol, hydralazine or nifedipine for controlling the blood pressure.[20,34] Out of these drugs, Methyldopa (0.5–3 g/day) is being used as initial therapy agent due to its ability to interact with presynaptic α_2-adrenergic receptors to diminish sympathetic outflow through the inhibition of norepinephrine release. By competing with dihydroxyphenylalanine during catecholamine biosynthesis, it reduces active neurotransmitter production, impairs baroreceptor function, and lowers blood pressure consistently.[12] Other agents, such as Nifedipine and hydralazine also helps in decreasing oxidative stress and suppressing pro-inflammatory mediators including MMP-13, IL-1β, IL-6, TNF-α, and COX-2.[40] While, drugs like clonidine, hydrochlorothiazide, nicardipine, and sodium nitroprusside are considered as the second line of treatment.[35] Since the severity of disease is associated with the frequent episodes of epileptic seizures, magnesium sulfate is used to prevent them owing to its neuroprotective and anticonvulsant properties.[36] However, the only definitive cure is considered to be the delivery of the fetus which entirely is decided by weighing the risks of ongoing disease against the benefits of continuing pregnancy for fetal maturity. This involves the use of supportive therapies for the fetal maturity and cautious fluid management. For example, corticosteroids are used for the fetal lung development in preterm pregnancies. The obstetrical and gynaecological societies have demonstrated that the low-dose of aspirin (ASA) can reduce the risk of PE by approximately 60% if initiated before 16 weeks of gestation. It acts by selectively diminishing thromboxane synthesis, sparing vasodilatory prostacyclin thereby promoting vascular homeostasis. Aspirin also modulates inflammatory signaling pathway via the inhibition of NF-κB activation.[37-39] These mechanisms appear particularly relevant during early placentation, a critical gestation time when dysregulation of these signalling may affect trophoblast invasion and disrupts maternal–fetal immunological crosstalk.

However, the interventions used for the regulation of vascular, endothelial and placental functions, have limited clinical efficacies. Currently, the placental and fetal delivery is considered to be the most effective cure of PE which further results in premature birth and increase in cases of neonatal morbidity.[41] Therefore, these limitations highlights a critical need for novel therapeutic approaches capable of targeting the molecular drivers of PE. In particular, there is an urgent need to find interventions that can prevent PE from developing or progressing before the appearance of overt clinical symptoms.[42]

In view of this, natural therapeutics derived from medicinal plants, have gained considerable global attention over the past decade, accompanied by the increasing use of herbal medicines. Both the natural isolated compounds as well as complex botanical extracts of these plants are often perceived as safer and more dependable alternatives to synthetic pharmaceuticals, largely due to their lower risk of adverse effects. They are rich in diverse phytoconstituents with antioxidant, anti-inflammatory, and vasoactive properties that has the ability to target multiple pathways involved in the pathophysiology of various diseases.[43] Therefore, they may offer a promising avenue for developing alternative and complementary therapies for the management of many ailments. Several pre-clinical or ex vivo studies on animal models of PE had identified nine plant-derived phenolic compounds as promising therapeutic agents for PE. The most intensively studied substances are resveratrol, quercetin, curcumin, salvianolic acid A (danshensu),

baicalin, epigallocatechin gallate, punicalagin, silibinin, and vitexin. Additionally, the complex botanical extracts derived from these plants like *Euterpe oleracea*, *Moringa oleifera*, *Punica granatum*, *Thymus schimperi*, *Uncaria rhynchophylla*, and *Vitis vinifera,* are also reported to have beneficial effects in preeclamptic animal models, highlighting their role as potential natural therapeutics in PE.[18] Among the identified plant-derived phenolic compounds, quercetin has emerged as a significantly promising compound because of its favourable safety profile and potent anti-inflammatory activities.[44] Evidence suggested that it exhibits anti-hypertensive properties, and confers protection against inflammation in both experimental models and clinical trials. Importantly, this flavonol has also shown to support the development of the embryo, fetus, and placenta without teratogenic and abortifacient effects.[42] Experimental studies have revealed that quercetin administration suppresses placental production of pro-inflammatory markers like TNF-α, IL-6, and monocyte chemo-attractant protein-1 (MCP-1), simultaneously reducing their circulating levels. As the pathogenesis of PE is strongly linked to the exaggerated inflammatory responses, these observations suggest that quercetin holds substantial potential for serving as therapeutic and preventive candidate for the management of this disorder, necessitating continued analysis into its full therapeutic potential.

QUERCETIN AND ITS MECHANISM OF ACTION

Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone), derived from the Latin word Quercetum meaning "oak forest," is a naturally occurring flavonol belonging to the family of flavonoids, that cannot be synthesized endogenously in human.[45] It appears as a yellow crystalline compound with hydrophobic and lipophilic characteristics demonstrating poor aqueous solubility but readily dissolves in alcohol and lipids, facilitating its incorporation into biological membranes. It is ubiquitously distributed in the plant kingdom and is among the most abundant dietary polyphenols with high content in onions, kale, apples, and berries.[46] Significant levels are also found in medicinal plants such as *Moringa oleifera* leaves, *Aloe vera* leaves, *Brassica oleracea* leaves, *Zingiber officinale* rhizome and leaves, *Acacia nilotica* bark, *Terminalia arjuna*, *Eugenia jambolana*, and *Azadirachta indica*.[47] It is predominantly present in glycosylated forms; following ingestion, these glycosides are hydrolyzed to the aglycone which is absorbed and metabolized into glucuronidated, sulfated, and methylated forms that mediates its systemic biological actions. Quercetin is one of the most widely studied bioflavonoids and has gained great scientific acceptance for its potential therapeutic use in the management of many inflammatory disorders including metabolic, neurologic, cardiovascular, hypertensive and pregnancy related problems. It has been reported as one of the most powerful naturally occurring antioxidants among polyphenols and exhibits a broad spectrum of pharmacological effects, including antiviral, antibacterial, anticarcinogenic, and anti-inflammatory actions. The major sources and biological properties of quercetin and its corresponding concentrations (mg/100 g) has been highlighted in Figure 1.[47,48]

Over the past decade, the use of quercetin, for the management of cardiovascular disease and hypertension has gained substantial attention because of its cardiometabolic protective effects. It employs vascular protective actions by refining endothelial function, augmenting the bioavailability of nitric oxide, and thereby decreasing endothelial injury induced by oxidative stress. It attenuates vascular inflammation and restricts atherogenic processes via the suppression of NF-κB signaling and inhibition of pro-inflammatory cytokines like TNF-α and IL-6. It has the ability to improve arterial compliance and blood pressure regulation by enhancing endothelium-dependent vasodilation, intonation of calcium dependent signalling and inhibition of angiotensin-converting enzyme activity.[14]

Additionally, it has also been shown that it possesses multifaceted benefits in the metabolic disorders such as diabetes and obesity by regulating the glucose and lipid metabolism and improving insulin sensitivity. It activates the AMP-activated protein kinase (AMPK) which further increase the glucose uptake, decrease the hepatic gluconeogenesis, thereby stimulating lipid oxidation. Quercetin is also reported to lessen the adipogenesis, reduce the chronic inflammation in adipose tissue, and increase the oxidative stress related to obesity. Collectively, these processes will result in improved metabolic profiles, lessen insulin resistance, and will safeguard against obesity-related problems like dyslipidemia and cardiovascular risk. In dyslipidemia, it is demonstrated to reduce the total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels while regulating high-density lipoprotein cholesterol. This mechanism is mediated by regulation of lipid-metabolizing enzymes, obstruction of lipid peroxidation, and promotion of lipoprotein's oxidation hence reducing the formation of foam cell and atherosclerotic plaque.

Quercetin also suppresses neuroinflammatory processes through downregulation of pro-inflammatory cytokines, including nitric oxide synthase (iNOS) and NF-kB, and thereby stimulating the regeneration of neurons for the reduction of lipid peroxidation and oxidative neuronal damage. Hence, it exhibits protective effects in neurological disorders by promoting the survival and regeneration of neurons beneficial in managing the neurodegenerative conditions which are primarily characterized by chronic inflammation and oxidative stress.

Moreover, quercetin also exhibits antiviral activities that inhibit many viral enzymes like polymerases, reverse transcriptase, proteases and DNA gyrase and also binds to the viral capsid proteins and thereby protect against the viral infection. It regulates leukocytes, and various intracellular signalling pathways involving kinases,

phosphatases, and membrane proteins critical to immune cell function for restoring the immune balance in the systemic and chronic inflammation.[61] It also enhances the expression of Th1-derived interferon-gamma (IFN-γ) and suppresses Th2-derived interleukin-4 (IL-4) production in peripheral blood mononuclear cells, enhancing a balanced immune profile in conditions of malnutrition and chronic inflammatory stress.[60] Moreover, it also exerts a membrane-stabilizing action on mast cells, inhibiting histamine, leukotrienes, prostaglandins, and other pro-inflammatory or allergic mediators' release in case of exaggerated inflammatory and allergic responses.[40]

Preclinical studies further indicate that quercetin has the ability to ameliorate key pathophysiological features of pre-eclampsia. Researchers had demonstrated that it can alter inflammatory cytokines such as IL-6, TNF-α, MCP-1-in both placental tissue and maternal circulation. In addition, it mitigates oxidative stress by decreasing lipid peroxidation markers including malondialdehyde and improves aberrant angiogenic signalling and endothelial dysfunction associated with PE.[71] Collectively, these pleiotropic actions highlight quercetin as a promising candidate for the prevention or management of PE owing to its combined anti-inflammatory, antioxidant, anti-oxidative-stress, antiangiogenic and endothelial-protective properties.

The therapeutic potential of quercetin and its derivatives across a wide range of disease conditions, including metabolic disorders, cardiovascular diseases, inflammatory and oncological conditions, neurological and respiratory disorders, viral infections, and pregnancy-related complications such as PE has been summarized in Table 1.

This highlights that quercetin can reduce placental and systemic inflammation, mitigate oxidative stress, improve angiogenic balance, and protect endothelial function. In light of these outcomes, quercetin may be targeted as a pleiotropic, multi- functional flavonol that can behave both as a supportive or preventive therapeutic agent in various life threatening diseases

POTENTIAL ROLE OF QUERCETIN IN PREECLAMPSIA

Over the past few years, the herbal compounds derived from the plants, have gained a notable worldwide focus, as supportive interventions for the management of pregnancy associated disorders. This widespread attention is highly influenced by the traditional practices and the urge to use potentially safer and natural therapies in pregnancy to overcome the adverse effects of traditional medicines. However, the use of these interventions is highly dependent on the philosophies of different populations about the traditional healthcare practices and also on the restricted pharmacological resources available for the treatment of these ailments.[67]

From this perspective, plant derived flavonoids have appeared as a significant favourable group of bioactive molecules that are suitable for use in pregnancy complications like preeclampsia. Several studies had reported their ability of regulating vascular integrity and endothelial homeostasis thereby emphasizing their antioxidant, anti-inflammatory, vaso relaxant, and antithrombotic properties making them relevant for the vascular dysfunction related diseases.[44] Since, PE is considered to be a multifactorial disease associated with abnormal placentation, systemic endothelial damage, low oxidative environment, and deregulated immune responses, the use of naturally occurring herbal medicines will exert protective effects in managing their clinical characteristics.[68]

In this framework, an extensively distributed dietary flavonoid, quercetin which is available in many fruits and vegetables (apples, berries, onions, green leafy vegetables, tea) as well as in numerous medicinal plants have emerged as a potential alternative medicinal candidate against the traditional medicine practices. Various studies have explored its biological profile to discover its therapeutic potential for managing the symptoms of PE either at the early or later stages of gestation. The anti-oxidative property of quercetin has demonstrated to stabilise the increased oxidative stress caused by placental hypoxia which in turn regulates the endothelial function and protects from the vascular damages.[64] It also has the capability to augment the bioavailability of endothelial nitric oxide required for the adequate vasodilation resulting in regulation of enhanced blood pressure. The numerous research studies highlighting the impact of quercetin on the management of pathological symptoms of PE have been tabularized in Table 2.

Additionally, it is also observed that the imbalance of immune and inflammatory systems, prevailed in PE, [69] is being regulated by quercetin due to its pronounced immune-modulatory activity. The dysfuntioning of placenta caused by improper activation of inflammatory pathways and compromised maternal immune tolerance results in adverse maternal outcomes.[70] This can also be regulated by the use of quercetin which mitigate the inflammatory signalling pathways by reducing the transcription of key inflammatory and immune mediators promoting a more balanced cellular environment in the placenta.

Hence, quercetin has a potential to support healthy placental development and to sustain a balanced immune response at the maternal-fetal interface.[71]

In the light of these evidences, it may be suggested that quercetin can be utilized as an adjunctive therapeutic approach to regulate the clinical outcomes of PE resulted due to discrepancies in the placental development and function. It may be represented as a biologically reliable and transnationally significant herbal compound for improving the outcomes of PE.

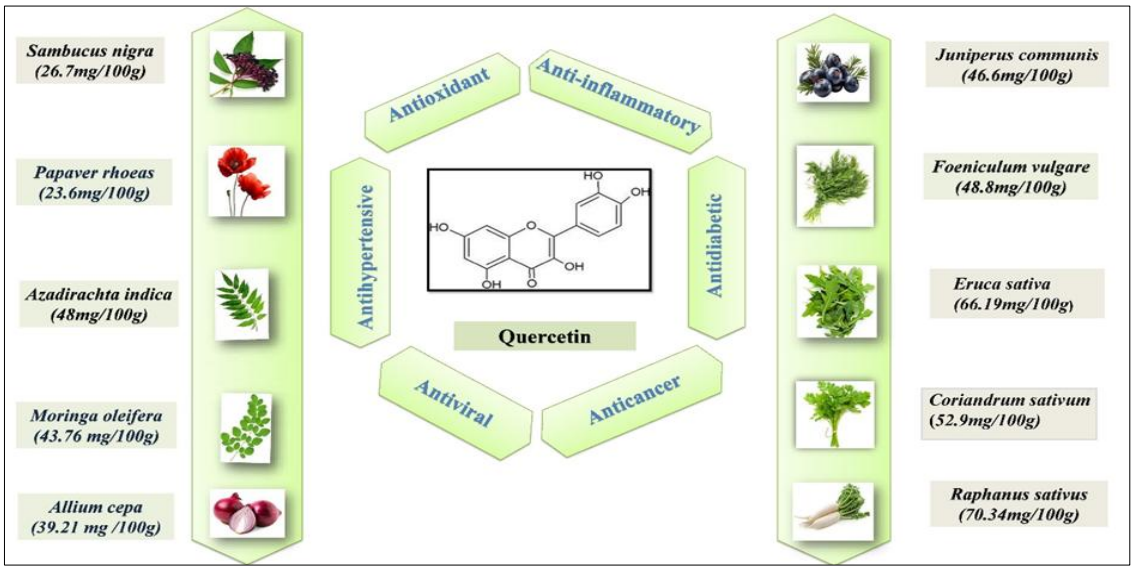

Figure 1: Plant sources and biological properties along with the concentrations per 100 g.

Table 1: The broad spectrum activity of quercetin in various disorders.

S. no.	Study model/type	Quercetin compound/ derivative and dose	Disease studied	Major finding	References
1	*In vivo* experimental studies in perinatal and protein restricted rat models.	Aglycone 50-200 mg/kg	Perinatal protein energy malnutrition	Reduction in stillbirth along with improvement in body weight was observed.	Sato et al, 2013[49]
2	*In vivo* experimental study in STZ induced mice	Aglycone	Gestational diabetes mellitus and diabetic embryopathy	Decrease in hyperglycaemia and oxidative stress in embryonic neural tissue was observed.	Cao et al, 2016[50]
3	*In vivo* animal model and *in vitro* mechanistic studies	Aglycone glycosides	General inflammation and immunity	Reduction in LPS leads to THE production of TNF-α, IL-1, IL-6, IL-8, along with reduction in reduced inflammatory and oxidative markers in models such as arthritis, experimental autoimmune encephalomyelitis, myocarditis, and spinal cord injury.	Li et al, 2016[53]
4	*In vivo* HFD mouse studies and *in vitro* adipocyte model	Aglycone	Obesity and metabolic syndrome	Reduction in inflammatory cytokines in adipose tissues was observed.	David et al, 2016[52]
5	*In vivo* animal model and *in vitro* neuronal studies	Aglycone	Neurodegenera-tive disease	Reduction in neuroinflammation was observed.	David et al, 2016[52]
6	RCT, *in vitro* antiviral studies.	Aglycone 500-1000 mg/day	Viral respiratory infections/URTI	In physically stressed population decrease in the incidence of upper respiratory tract infections were observed.	Li et al, 2016[53]
7	*In vitro* and *in vivo* preclinical studies.	Aglycone	Cancer	Apoptosis through intrinsic and extrinsic pathways was observed.	Hashemzaei et al, 2017[54]
8	*In vivo* study in diabetic gestational mice	Aglycone 30 mg/kg	Diabetic fertility/ implantation defects	Improvement in glycaemic control was observed along with serum estradiol levels. Also, there was	Bolouki et al, 2020[51]

Continued.

S. no.	Study model/type	Quercetin compound/ derivative and dose	Disease studied	Major finding	References
				also normalization of estradiol/ progesterone ratio.	
9	Rat models of LPS-LNAME and	Aglycone 2-50 mg/kg	PE	Reduction in diastolic blood pressure and proteinuria was observed along with reduction in placental oxidative damage and inflammatory mediators. There was also improvement in the pregnancy outcomes such as placental weight. Fetal resorption, birthweight, and early survival of neonatal.	Li et al, 2020[16]
10	*In vitro* experimental studies in HFD pregnant rodents	Aglycone (1% w/w or 50-200 mg/kg)	HFD induced maternal overweight/dyslipidaemia	Reduction in HFD induced dyslipidaemia was observed along with reduction in oxidative stress and proinflammatory cytokines with increase in glucose insulin and lipid profiles.	Li et al, 2020[16]
11	Rodent pregnancy model	Aglycone 5-200 mg/kg	Maternal obesity, dyslipidaemia hypertension	Improvement in nitrosative and oxidative stress marker was observed.	Costa et al, 2022[55]
12	Randomized control human trials	Aglycone 150-1000 mg/day	Cardiovascular disease	Reduction in systolic BP in hypertension or overweight subjects was observed.	Zhang et al, 2023[56]
13	Pre-clinical and *in vivo* studies in STZ induced diabetic rodents.	Aglycone	T2DM	Reduction in lower FBG along with improved glucose tolerance was observed	Ansari et al, 2023[57]
14	Meta analyses, small randomized clinical trials	Aglycone 500-1000 mg/day	Human T2DM	Reduction in FBG, Oxidative stress and some lipid parameter was observed.	Mugisha et al, 2025[58]
15	Early phase human pilot studies	COPD	Aglycone 1000 mg/day	Reduction in the inflammation of lungs and oxidative stress were observed.	Jagru et al, 2025[59]

BP: Blood pressure; COPD: chronic obstructive pulmonary disease; HFD: high-fat diet; LPS: lipopolysaccharide; L-NAME: NG-nitro-L-arginine methyl ester; PE: pre-eclampsia, RCTs: randomized controlled trials; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; URTI: upper respiratory tract infection

Table 2: Experimental studies highlighting the effect of quercetin in preeclampsia.

S. no.	Study type/model	Intervention	Comparator	Key outcomes	References
1	Pre-clinical L-NAME-induced PE rat model	Quercetin (2 mg/kg BW/day, GD4-19) + aspirin (1.5 mg/kg BW/day, GD4-19)	Low dose of Aspirin (1.5 mg/kg BW/day) as a control	Enhanced aspirin effects with decrease SBP and proteinuria along with decrease in uterine VEGF/sFlt-1 MRNA with increase in the survival of pup was observed.	Yang et al, 2019[60]
2	*In vitro*/*ex-vivo* PE placental Hypoxia model	Quercetin (3 µM), Mito Q (1–8 µM) under hypoxic condition	Normoxic (21% O_2) as control	Increase in the oxidative stress inflammation or apoptosis in placental explants. Placental hypoxia drives the PE endothelial dysfunction. Restoration of normoxic levels/mt DNA when administered with MitoQ (1 µM)+quercetin (3 µM)	Vangrieken et al, 2021[61]

Continued.

S. no.	Study type/model	Intervention	Comparator	Key outcomes	References
3	LPS induced PE-like SD rat model/ preclinical *in vivo* inflammation-based PE model.	Quercetin, 2 mg/kg BW (GD6-18, i.p.); + aspirin 1.5 mg/kg BW (GD 6-18, oral)	Aspirin (1.5 mg/kg) BW	Decrease in proteinuria, restoration of sFLt-1/P1GF balance along with increase in IL-10 was observed.	Yang et al, 2022[62]
4	*In vitro* Be Wo choriocarcinoma trophoblast cells oxidative stress model	Quercetin (5 µM)	CAMP/forskolin-induced synctiallisatio-n as positive control	Increase in trophoblast fusion and mitochondrial function via a SIRT1-dependent pathways was observed.	Yoshida et al, 2024[63]
5	LPS induced PE like STZ rat model	Quercetin 2 mg/kg BW (GD6-18, i.p.) + Aspirin 1.5 mg/kg BW (GD6-18, oral)	Aspirin alone (1.5 mg/kg BW)	Increase in placental NLRP3 inflammasome with decrease in sFlt-1: PIGF ratio, decrease in IL-6, increase in IL-10, decrease in SBP, proteinuria was observed.	Ding et al, 2024[64]
6	Human PE placenta and hypoxia model	Quercetin, 3 µM (24 hours for Be Wo cells)	Hypoxia, Mito Q, 1 µM	Reduction in hypoxia was observed.	Vangrieken et al, 2024[65]
7	*In vitro* erastin induced HUVEC endothelial dysfun-ction and *in vivo* SRUPP rat PE model	Quercetin (3-5 µM)	Erastin or DMSO	Decrease in BP/proteinuria, along with improved placental vessels and angiogenesis was observed.	Shi et al, 2025[66]

BW: Birth weight; BP: blood pressure; GD: gestational day; HUVEC: human umbilical vein endothelial cells; Flt-1: soluble fms-like tyrosine kinase-1, PE: PE; SBP: systolic blood pressure, STZ: streptozotocin induced diabetic rats, sRUPP: surgically reduced uterine perfusion pressure; SD: Sprague Dawley: L-NAME: NG-nitro-L-arginine methyl ester, LPS: lipopolysaccharides: PlGF: placental growth factor, VEGF: vascular endothelial growth factor

CONCLUSION

PE remains the leading cause of maternal and neonatal mortality and morbidity across the globe. The hallmark characteristics are considered to be deregulated immune system, oxidative stress, improper endothelial function, and angiogenic imbalance. Despite of extensive research to explore the underlying mechanism of this disorder, its exact pathophysiology is still elucidated. Moreover, the available management strategies are mainly focused on curating the symptomatic characteristics instead of improvising the root cause of the disease. Also, the current pharmacological treatment system has limitations because of their adverse effects in the pregnancy. Together, this necessitates the development of safe and efficacious therapeutic as well as management strategies targeting the complex pathology of PE without compromising maternal and foetal health. In this context, naturally occurring dietary flavonol, quercetin has gained global importance to be used as a potential therapeutic agent due to its versatile pharmacological behaviour. It possesses antioxidant, anti-inflammatory, and Immuno-modulatory properties that has the capability to decrease the oxidative stress and the levels of inflammatory transcriptional moderators that may regulate endothelial homeostasis and immune tolerance in PE. However, the preclinical facts about quercetin seems promising, its clinical translation is yet to be elucidated. Further studies can also be planned to delineate its pharmacokinetic characteristics including optimal dosage and long term security during pregnancy. By augmenting its bioavailability with innovative approaches like nanoparticle or liposomal delivery systems in large scale randomized trials, its therapeutic potential can further be improved. In light of these points, it may be stated that quercetin may be considered as an alternative to current therapeutic and management strategies of PE for providing a stable immunological environment for the successful progression of pregnancy.

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