Review

DOI: 10.5582/ddt.2025.01059

Quercetin as a multifaceted therapeutic agent in recurrent pregnancy loss: Mechanisms and clinical perspectives

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SUMMARY: In recent years, there has been an escalating incidence of recurrent pregnancy loss (RPL), imposing substantial psychosocial and economic burdens on families. Despite extensive investigations, approximately 50% of cases remain idiopathic, underscoring the intricate nature of potential pathogenic mechanisms. Quercetin (QUE), a prevalent flavonoid compound, exhibits potential in the therapeutic modulation of RPL by influencing endocrine, coagulation, oxidative stress, inflammation, and immune responses. This review aims to elucidate the potential role of QUE in RPL, explore its molecular mechanisms, and delineate its therapeutic significance. Herein, we synthesize existing evidence on the impact of QUE in RPL, particularly in traditional Chinese medicine, accentuating areas necessitating further exploration. QUE demonstrates regulatory prowess over RPL by modulating endocrine functions, encompassing thyroid functionality, diabetes, polycystic ovary syndrome, and luteal phase defects. It exhibits anti-inflammatory and antioxidant properties, influences coagulation functions, and affects immune cells such as T cells, T helper cells, macrophages, and natural killer cells. QUE also interacts with maternal-fetal interface cells, including myeloid-derived suppressor cells, stromal cells, and extravillous trophoblast cells, highlighting its multifaceted role in the modulation of RPL. Despite promising preclinical data, clinical trials directly targeting RPL remain limited. We emphasize the need for rigorous human studies to validate QUE's efficacy and safety in pregnancy. By elucidating the mechanistic underpinnings of QUE in treating RPL, this research may contribute to developing targeted interventions for RPL and other adverse pregnancy conditions, ultimately ameliorating reproductive health and well-being for affected individuals and families.

Keywords: endocrine, coagulation, inflammation, oxidative stress, maternal-fetal interface

1. Introduction

Recurrent pregnancy loss (RPL) is defined as the occurrence of two or more consecutive fetal losses with the same sexual partner before 28 weeks of gestation. With the increasing trend of women delaying childbirth and the implementation of policies such as China's "comprehensive two-child" and "three-child" policies, the incidence of RPL has been rising each year (*1*). It has become a significant health issue both nationally and globally. Globally, RPL affects 1–5% of couples, with rising incidence linked to delayed childbearing. The etiology of RPL is complex and diverse, and its clinical manifestations are nonspecific, making the diagnosis and treatment challenging. The treatment of RPL mainly focuses on addressing the causative factors and managing symptoms. The routine use of low molecular weight heparin, either alone or in combination with low-dose aspirin, may be prescribed during early pregnancy for RPL patients with positive thrombophilia screening (PTS), aiming to improve pregnancy outcomes. Assisted reproductive technology can also be utilized to address fertility issues caused by chromosomal abnormalities in RPL patients, among other treatments. However, some of these treatments can be costly and may result in adverse effects such as bleeding, gastrointestinal reactions, liver function abnormalities, and allergies. Moreover, the overall efficacy of these treatments is not always satisfactory. It is important to continue researching and exploring more effective and safer treatment options for RPL to improve patient outcomes and reduce the burden of this condition.

Traditional Chinese medicine (TCM) has a long history and extensive experience in treating RPL. Quercetin (QUE) is a flavonoid compound in everyday vegetables and fruits such as red onions, apples, broccoli, red grapes, and citrus. It is also present in various TCMs like santolina, scutellaria baicalensis, and acacia (*2*). Chemically, it is known as 3,3',4',5,7-pentahydroxyfla vonoids, with a molecular formula of $C_{15}H_{10}O_7$. Figure 1 depicts its structural formula. QUE exhibits favorable therapeutic efficacy, low toxicity, and multiple biological functions. It acts as an antioxidant, anti-inflammatory agent, chelator of iron, and regulator of lipid metabolism (*3,4*). In addition, QUE has been shown to have relatively few toxic side effects. However, in terms of treating RPL, despite the promising research prospects of QUE, clinical trial data directly targeting RPL remains scarce. To address this gap, we can draw inspiration from the ancient and rich repository of TCM. Many of these formulas contain herbs rich in QUE, such as *Cuscuta sinensis* and *Sambucus nigra* (*5,6*). These herbs have a long history of tonifying the kidneys, securing the fetus, and regulating reproductive health, contributing to improved pregnancy outcomes (*7*). In conclusion, investigating the potential role of QUE in RPL and understanding its associated mechanisms could offer new insights into this condition's clinical prevention and treatment.

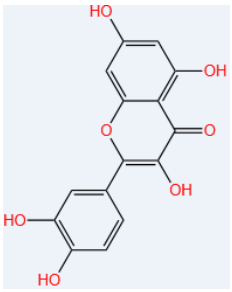

Figure 1. The structural formula of quercetin.

2. Clinical treatment containing QUE

In modern clinical practice, TCMs frequently used to prevent miscarriage include Yi Qi Bu Shen Fang (*8*) and Shou Tai Wan (*9*). Zi Shen Yu Tai pill employs *Cuscuta chinensis* to fortify the kidneys and secure the fetus, with additional herbs like *Taxillus chinensis*, *Dipsacus asperoides*, and *Eucommia ulmoides* to bolster kidney Yang and Qi. *Codonopsis pilosula* and *Atractylodes macrocephala* augment Qi and strengthen the Pi, while *Rehmannia glutinosa* and *Lycium barbarum* nourish the blood and calm the fetus. This formula has been shown to effectively alleviate traditional Chinese medical symptoms during pregnancy and elevate serum progesterone levels (*10,11*). Similarly, Jia Wei Shou Tai pill prominently features *Cuscuta chinensis*, complemented by *Dipsacus asperoides*, *Taxillus chinensis*, and donkey-hide gelatin, to improve levels of progesterone and human chorionic gonadotropin during pregnancy (*12*). In these miscarriage-preventing formulas, *Cuscuta chinensis* and *Taxillus chinensis* often play a crucial role, with QUE identified as a significant active component in these kidney-tonifying herbs through liquid chromatography-mass spectrometry (*13,14*), sparking interest in their potential to enhance pregnancy outcomes.

Innovations upon traditional prescriptions for treating RPL have led scholars to develop the "Bushen-Yiqi-Lixue-Yangtai" (BYLY) compounds used to prevent and treat RPL (*15*). A clinical trial with 480 patients revealed that the combination of Duphaston and BYLY markedly reduced early miscarriage rates compared to BYLY or Duphaston alone, suggesting significant benefits and improved pregnancy outcomes. This regimen incorporates various herbs rich in QUE, such as *Paeonia lactiflora* Pall. and *Cuscuta chinensis*. The mass spectrometry analysis verified that the key component of the compound above is QUE. Besides, network pharmacology studies further identified QUE as a key molecule in BYLY's treatment of RPL, and cellular experiments showed that QUE enhanced the biological function of trophoblast cells under hypoxic conditions. This clinical evidence from widely used herbal medicines underscores QUE's potential as a therapeutic agent for RPL. Table 1 summarises clinical trials involving QUE for the treatment of RPL, where the key component of the primary drugs used in the clinical trials is QUE (*10,15-20*). These clinical studies have limited sample sizes and exhibit heterogeneity in herbal formulations, indicating that QUE's therapeutic use requires more direct clinical validation (*21*).

3. QUE improves endocrine function

Endocrine dysfunction plays a significant role in the occurrence of RPL, with approximately 8% to 12% of endocrine alterations associated with RPL (*22,23*). Although various endocrine factors can cause RPL, many underlying mechanisms remain unclear. Several endocrine disorders have been identified as possible contributors to RPL, including thyroid dysfunction, diabetes, polycystic ovary syndrome (PCOS), and luteal insufficiency. These conditions can adversely affect oocyte quality and endometrial tolerance, increasing the risk of RPL. Additionally, they may induce a prothrombotic state, further elevating the likelihood of experiencing recurrent miscarriage.

3.1. QUE regulates thyroid function

Maternal influences on the production, secretion, and metabolism of thyroid hormone (TH) during pregnancy can significantly increase the incidence of thyroid disease (*24*). Abnormal thyroid function has been found to affect

Table 1. Clinical trials using QUE-containing drugs for the treatment of miscarriage

No.	Research Title	Experimental Design	Sample Size	Medicine	Experimental Period	Results
1	Zishen yutai pill as an adjuvant therapy in threatened Miscarriage: A meta-analysis of 23 randomized controlled trials (*10*)	Meta-analysis	2411	Zishen yutai pill & Western medicine	14d	Significantly improved human chorionic gonadotropin, the total effective rate, progesterone, estradiol, abdominal pain, vaginal bleeding, and fibrinogen
2	The effect of a traditional Chinese quadri-combination therapy and its component quercetin on recurrent pregnancy loss: A clinical trial, network pharmacology, and experiments-based study (*15*)	RCT	480	Duphaston & BYLY	14-28d	The early miscarriage rate was 10.62% in the Duphaston+BYLY group, 29.17% in the BYLY group, and 29.06% in the Duphaston group
3	Clinical Efficacy of Bushen Antai Decoction in Patients with Kidney Deficiency-Type RPL (*16*)	RCT	260	Bushen Antai Decoction & Dydrogesterone	<12 weeks in gestational age	The integrated group reached 93.1%, the pure TCM group 74.4%, and the pure Western medicine group 73.6%
4	Effect of Yiqi Bushen & Progesterone on RPL in Kidney Deficiency Threatened Abortion and Hormone Levels (*17*)	RCT	102	Yiqi Bushen & Progesterone	14d	The research group's fetal protection rate was 93.88%, higher than the control's 79.17%
5	Clinical Observation on the Treatment of RPL-PTS by Bushen Huoxue Recipe (*18*)	RCT	146	Bushen Huoxue Recipe & Low molecular weight heparin.	<12 weeks in gestational age	The integrated group reached 90.9%, the pure TCM group 74.4%, and the pure Western medicine group 52.6%
6	Efficacy of Modified Shoutai Pill in the Treatment of RPL and Its Impact on Coagulation Function and Th17 Cell-Related Factors (*19*)	Retrospective study	120	Modified Shoutai Pill & Progesterone	<12 weeks in gestational age	The research group's effective rate was 90.48%, higher than control's 75.44%
7	Effect of Jiawei Shoutai pills combined with dydrogesterone on pregnancy outcome of kidney-deficiency early threatened abortion after tocolytic therapy (*20*)	RCT	92	Jiawei Shutai Pill & Dydrogesterone	14d	The research group's fetal protection rate was 95.65%, higher than the control's 80.43%

pregnancy outcomes at both endocrine and immune levels and is considered a risk factor for RPL (*25*).

3.1.1. Hyperthyroidism

Hyperthyroidism increases the risk of RPL. Excessive TH in the bloodstream can lead to increased neuromuscular excitability, elevated secretion of norepinephrine and angiotensin, vasospasms, and contractions, ultimately resulting in miscarriage (*26*). QUE has been found to directly inhibit hyperthyroidism by activating the Nrf2 signaling pathway. Furthermore, QUE exhibits antihypertensive effects and acts as an effective angiotensin-converting enzyme inhibitor (ACEI), further mitigating vascular and contractile complications associated with hyperthyroidism. Besides, QUE also influences TH metabolism by inhibiting deiodinases, enzymes critical for TH activation (*27*). These findings highlight the potential therapeutic benefits of QUE in addressing thyroid-related reproductive complications.

3.1.2. Hypothyroidism

Hypothyroidism is often associated with hypoprolactinemia, which can lead to follicular hypoplasia and luteal insufficiency (*28*). This results in inadequate production of steroid hormones, which are necessary to maintain the endometrium during the secretory phase. Insufficient hormonal support can lead to early miscarriage. Studies have shown that QUE exhibits an anti-thyroid effect by inhibiting thyroid cell growth and suppressing the expression of key thyroid-related proteins, including the sodium/iodide symporter, thyroglobulin, thyroid peroxidase, and thyroid-stimulating hormone receptor (*29*). Although no studies have specifically investigated QUE's effects in hypothyroidism models, it is hypothesized that QUE may exacerbate hypothyroidism. Therefore, the severity of hypothyroidism should be carefully evaluated when considering QUE in clinical applications.

3.2. Diabetes

Diabetes, whether in the form of pre-existing diabetes combined with gestational syndrome or gestational diabetes mellitus, is a common metabolic disorder that can have significant impacts on pregnancy outcomes. Insulin resistance (IR) is a characteristic feature of diabetes where the body's response to insulin is reduced, leading to elevated blood glucose levels and compensatory hyperinsulinemia (*30*). Poor control of blood glucose during pregnancy increases the risk and incidence of RPL, as well as adverse clinical outcomes for both the mother and infant (*31*). QUE has been extensively studied for its potential therapeutic effects on diabetes. Numerous studies have reported its antidiabetic activity (*32-35*), primarily due to its ability to improve IR. QUE has shown efficacy in significantly improving insulin sensitivity and glucose uptake. Additionally, QUE has been found to enhance oocyte and embryo quality in diabetic mouse models (*36*) and improve endometrial tolerance (*37*) in the diabetes animal model.

3.3. Polycystic ovarian syndrome (PCOS)

PCOS is an endocrine disorder that serves as a risk factor for RPL. Hyperinsulinemia/IR, high androgen levels, and obesity are the main factors contributing to RPL in individuals with PCOS. Studies have shown the therapeutic effects of QUE in animal models of PCOS (*38,39*). QUE has demonstrated significant attenuation of PCOS-induced IR, sex hormone disorders, and ovulatory abnormalities. In addition to hyperinsulinemia/IR, high androgen levels, and obesity, other factors such as elevated luteinizing hormone (LH) levels, hyperhomocysteinemia, and a prethrombotic state complement reinforce the development of RPL in PCOS. QUE has been found to possess inhibitory effects on LH levels (*40*). Although there are no specific reports on the association between QUE and hyperhomocysteinemia, some studies have indicated that QUE protects against homocysteinemia-induced oxidative stress in rats (*41*). These findings suggest a potential positive role for QUE in managing hyperhomocysteinemia.

3.4. Potential effects of QUE in luteal phase defect (LPD)

LPD is closely associated with miscarriage and is characterized by reduced endometrial secretory responsiveness caused by issues such as post-ovulatory luteal dysplasia, insufficient progesterone secretion, or premature degeneration of the corpus luteum (*42*). LPD leads to a decreased ability of the endometrium to support implantation and maintain pregnancy. Although there are limited reports on the association between QUE and LPD, researchers have conducted studies using a Bu-shen-zhu-yun decoction in rats, significantly improving LPD. It is worth noting that the serum level of QUE was elevated in the treatment group compared to the rats in the control group (*43*), suggesting that QUE may have beneficial effects in improving LPD and potentially reducing the risk of RPL by addressing the underlying factors contributing to LPD.

3.5. Potential effects of QUE in hormone supplementation

The researchers discovered that supplementation of progesterone, progestogen, and human chorionic gonadotropin can reduce the abortion rate in patients with RPL and increase the live birth rate (*44,45*). QUE has been shown to upregulate steroid hormone levels and improve ovarian function (*46*), indicating its potential role in hormone modulation. Notably, reports indicate

that QUE can promote the release of progesterone and progestogen from ovarian granulosa cells (*47,48*) and stimulate progesterone release from preovulatory follicles (*49*). These findings highlight the promising role of QUE in hormonal regulation and its potential as a therapeutic approach for individuals with RPL.

Individuals with a history of RPL undergo comprehensive endocrine evaluations to identify any underlying hormonal abnormalities and address them accordingly. Based on the existing research foundation, it can be speculated that QUE may help regulate endocrine function and reduce the risk of complications associated with RPL (Figure 2).

4. QUE improves coagulation

PTS, characterized by increased blood coagulation and a higher risk of thrombus formation, has gained significant attention in its association with RPL. While there is currently a lack of specific reports on the relationship between QUE and the prethrombotic state, a review of the literature reveals that QUE has demonstrated the ability to inhibit the mRNA level of plasminogen activator inhibitor 1, a key substance involved in the prethrombotic state. This inhibitory effect has been observed in a dose- and time-dependent manner (*50,51*), suggesting a potential role for QUE in inhibiting the process of thrombus formation. In addition, some studies have reported the regulatory role of QUE in coagulation function. For example, in treating patients with COVID-19, QUE can reduce coagulation abnormalities and inhibit thrombosis by inhibiting blood protein disulfide isomerase (*52*). In a neonatal asthma rat model, QUE can protect neonatal asthma by reducing coagulation time and coagulation factor activity (*53*). These findings highlight the potential of QUE as both a preventive and therapeutic agent in modulating coagulation processes and mitigating complications associated with PTS and related conditions.

5. QUE's antioxidant properties

QUE is a potent free radical scavenger among flavonoids. Due to the presence of phenolic hydroxyl groups and double bonds, it exhibits significant antioxidant activity (*54*). The catechol group on the B ring and the hydroxyl group at position three on the A ring collectively contribute to QUE's antioxidant characteristics (*55*). The hydroxyl groups in QUE's structure deactivate free radicals by donating active hydrogen, thereby oxidizing and stabilizing them, preventing unsaturated fatty acid oxidation (*56*). Due to its chemical structure, QUE can scavenge various free radicals, including ROS, RNS, H_2O_2, superoxide, and hydroxyl radicals (*57*). Oxidative stress levels are elevated in the plasma and placentas of patients with RPL (*58*), and researchers speculate that oxidative damage caused by increased production of oxidative substances and weakened antioxidant defenses might contribute to RPL (*59*). Compared to the control group, women with recurrent miscarriages show increased spontaneous chemiluminescence in granulocytes, confirming heightened leukocyte free radical production (*60*). Plasma samples from patients with RPL also show a marked increase in superoxide anion radicals and H_2O_2 (*61*). These findings suggest that QUE may potentially ameliorate oxidative stress in patients with RPL.

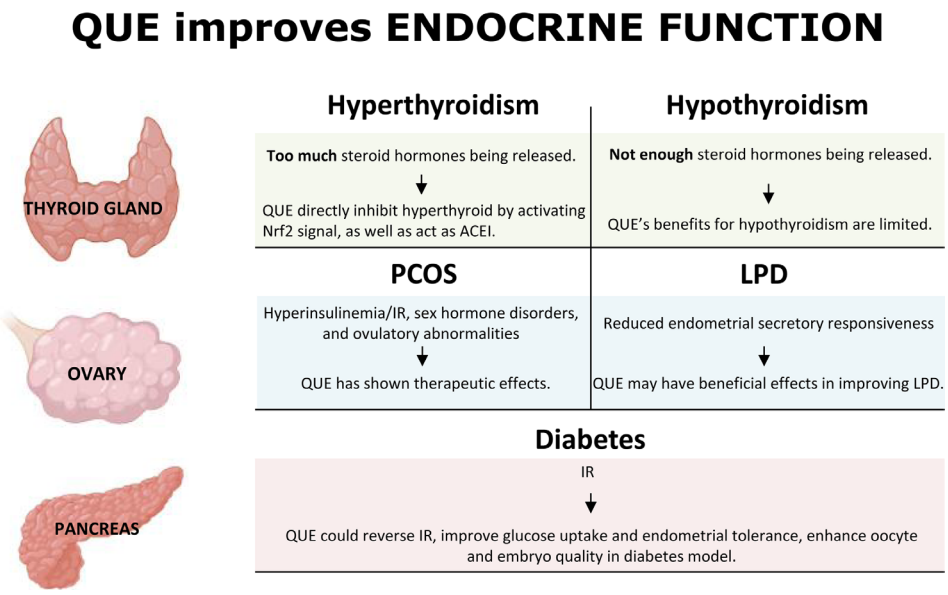

Figure 2. Mechanisms of quercetin in improving endocrine function in various conditions relevant to recurrent pregnancy loss. QUE: quercetin; Nrf2: nuclear factor erythroid 2-related factor 2; ACEI: angiotensin-converting enzyme inhibitor; PCOS: polycystic ovary syndrome; LPD: luteal phase defect; IR: insulin resistance.

6. QUE regulates gut microbiota

Dysbiosis of the gut microbiota is increasingly recognized as a potential risk factor for inflammation and the development of autoimmune and immune-mediated diseases. In patients who have experienced miscarriage, serum levels of interleukin 2 (IL2), IL17A, IL17F, tumor necrosis factor alpha (TNF alpha), and interferon gamma (IFN gamma) are significantly elevated, indicating a predisposition toward inflammation through Th1 and Th17-mediated immunity (*62*). A randomized controlled study analyzing fecal microbiota revealed a marked reduction in microbial diversity and the relative abundance of *Prevotella_1*, *Prevotellaceae_UCG_003*, and *Selenomonas_1* in RPL cases, which leads to a decrease in inducible Tregs and the activation of pro-inflammatory cells. This research further suggests a correlation between reduced gut microbial diversity and increased pro-inflammatory cytokines in miscarriage patients (*63*).

QUE has been reported to enhance gut microbial diversity and restore microbial symbiosis, thereby alleviating colitis in mouse models of *Citrobacter rodentium* infection and dextran sulfate sodium salt-induced colitis (*64,65*). Specifically, QUE supplementation promotes the enrichment of *Bacteroides*, *Bifidobacterium*, *Lactobacillus*, and *Clostridium*, while significantly reducing the abundance of *Fusobacterium* and *Enterococcus*, indicating a profound impact on the composition of the gut microbiota (*66*).

Although no studies have directly investigated the effects of QUE on the gut microbiota of RPL patients, given its ability to restore gut microbial balance and the crucial role of gut microbiota in shaping and regulating the immune system and immune responses, QUE may potentially alleviate RPL by modulating the gut microbiota. While QUE restores gut microbiota in colitis models, its role in RSA-related dysbiosis remains speculative. Future studies should profile fecal microbiota in RSA patients pre/post-QUE intervention.

7. QUE regulates inflammatory responses and immune cells

7.1. QUE's anti-inflammatory properties

Chronic endometritis (CE) is a persistent, mild inflammation of the endometrium. Although a subtle condition, the prevalence of CE is notably higher in women with infertility, implantation failure, and RPL (*67,68*). Women with a history of RPL and untreated CE show a very low live birth rate (7%). However, after treatment and resolution of CE, the sustained pregnancy rate significantly improves (*69*).

Various studies on cell and animal models have demonstrated that QUE possesses anti-inflammatory properties. *In vitro* research on guinea pig epithelial cells revealed that QUE inhibits the production of pro-inflammatory enzymes, such as cyclooxygenase and lipoxygenase (*70*). The anti-inflammatory activity of QUE is primarily attributed to its ability to suppress pro-inflammatory cytokines, such as nuclear factor kappa B, TNF alpha, IL 6, and IL1 beta, and inflammatory mediators like catalase and nitric oxide (*71*). In cases of CE, the overexpression of IL1 beta, IFN gamma, and TNF alpha suggests that QUE may alleviate CE by inhibiting the expression of these pro-inflammatory factors, ultimately improving sustained pregnancy rates.

In vitro studies indicate that QUE exhibits both anti-inflammatory and immune-enhancing effects. However, a double-blind, placebo-controlled, randomized trial revealed that, although daily supplementation with 500 or 1000 mg of QUE for 12 weeks significantly increased plasma QUE levels in adult women in the UK community, it had no impact on innate immune function or inflammatory markers. Further validation is needed to confirm QUE's role as an immune modulator in humans (*72*).

7.2 QUE regulates immune cells

The immune system plays a crucial role in maternal-fetal immune tolerance, which is necessary for a successful pregnancy. Abnormalities in immune cells, specifically T cells, dendritic cells (DCs), macrophages, and natural killer (NK) cells, have been implicated in RPL (Figure 3).

7.2.1. T cells

T-cell receptors stimulate the differentiation of primitive $CD4^+$ T cells into specific subsets, such as T helper 1 (Th1), Th2, Th7, Th17, Th22, and follicular Th cells, each playing a distinct role in pregnancy (*73*). Imbalances in the Th1/Th2 ratio, with an increase in Th1 cells and a decrease in Th2 cells, may contribute to recurrent miscarriage. Th1 cells release pro-inflammatory factors like IFN gamma and TNF beta, promoting inflammation at the maternal-fetal interface (*74*). Maintaining a standard Th17/Treg ratio is essential for a healthy pregnancy. Imbalances in this ratio have been associated with early recurrent miscarriages (*75,76*). Treg cells exhibit anti-inflammatory and immunosuppressive effects through cytokine secretion and contact-dependent inhibition, while Th17 cells release pro-inflammatory factors like IL17, IL6, IL22, and TNF alpha. Existing studies suggest that QUE can improve the balance of Th1/Th2 (*77,78*) and Th17/Treg (*79,80*) ratios in various allergic diseases, indicating its potential benefit in RPL by modulating T cell function.

7.2.2. DCs

DCs, accounting for approximately 1% to 2% of immune cells in the metaphase, serve a dual role as powerful antigen-presenting cells and activators of

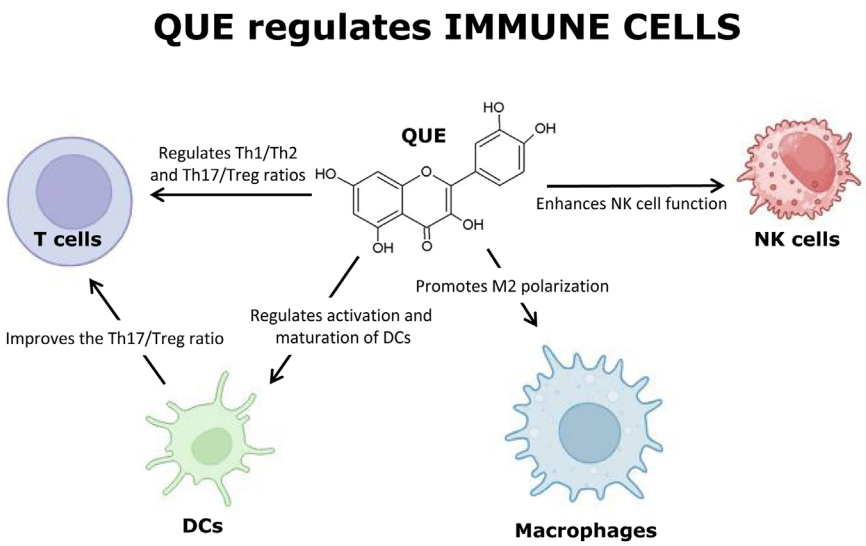

Figure 3. Immunomodulatory effects of QUE on key immune cells in recurrent pregnancy loss. QUE: quercetin; DCs: dendritic cells; NK: natural killer; Th: T helper.

effector T cells to mediate cellular immune responses. Immature DCs can promote immune tolerance by inducing the generation of differentiated Tregs. Research has confirmed the significant role of DCs in maternal recognition of paternal antigens (*81*). In response to specific cytokines like GM-CSF, IL-4, IL-10, TGF beta, and IDO, decidual DCs acquire a tolerogenic phenotype known as tolerogenic DCs. These tDCs are capable of driving Th0 cell differentiation into Tregs. Additionally, DCs have been shown to promote the differentiation and proliferation of endometrial mesenchymal stromal cells and local angiogenesis (*82*). In the relevant literature, QUE has been reported to possess inhibitory effects on the activation and maturation of DCs, thereby exhibiting anti-inflammatory properties and preventing the progression of atherosclerosis (*83*). Based on these existing reports, it can be hypothesized that QUE may inhibit the inflammatory response in RPL by directly acting on DCs. Furthermore, QUE might benefit RPL by influencing T cells through DCs, promoting their differentiation into Tregs, and improving the Th17/Treg ratio.

7.2.3. Macrophages

Macrophages can be categorized into M1 and M2 subtypes, with M1 promoting inflammation and M2 supporting normal pregnancy. The balance between M1 and M2 macrophages is crucial for maintaining pregnancy (*84*). At the maternal-fetal interface, the ratio of M1/M2 macrophages changes during different stages of pregnancy. Initially, M1-type macrophages predominate in the periamputation period, then transition to a mixed population of M1 and M2 macrophages. After the establishment of the placenta, M2-type macrophages become dominant (*85*). An imbalance, with a significant increase in M1-type macrophages or a decrease in M2-type macrophages, can lead to RPL (*86*). QUE has been reported to inhibit M1-type macrophage polarization and promote M2-type macrophage polarization, suggesting its therapeutic potential in inflammatory disorder-related diseases (*87*).

7.2.4. NK cells

NK cells are present in various sites within the female reproductive system, including cNK cells in peripheral blood, trNK cells in tissues, and uNK cells in the uterus, primary immune cells at the maternal-fetal interface, and crucial for early embryonic development. Abnormalities such as excessive aggregation of uNK cells in early pregnancy, abnormal cytotoxicity, or decreased secretion of growth-promoting factors by cNK and metaphase NK cells can contribute to RPL (*88-90*). Although specific reports on the relationship between QUE and NK cells at different sites are limited, existing studies have indicated that QUE can enhance NK cell function (*91,92*). This suggests the potential therapeutic role of QUE in regulating NK cell function and its potential benefit in RPL.

While the existing literature supports the notion that QUE may modulate the function of immune cells, further research is needed to fully understand the mechanisms and evaluate the efficacy of QUE in managing immune cell abnormalities associated with RPL.

8. QUE regulates other cells at the maternal-fetal interface

8.1. Decidual myeloid-derived suppressor cells (MDSCs)

Myeloid-derived suppressor cells are a novel, heterogeneous group of immunosuppressive cells originating from myeloid progenitors and can be subdivided into monocytic and granulocytic subtypes. In the murine decidua, they are second in abundance

only to uterine NK cells (*93*). Various factors, such as estrogen, progesterone, hypoxic conditions, the HLA-G/ILT4 signaling axis, as well as the STAT3 and CXCR2 signaling pathways, collectively promote the differentiation and accumulation of MDSCs at the maternal-fetal interface (*94*). MDSCs maintain immune tolerance at this interface by inhibiting the proliferation of DCs and T cells and by promoting the generation of Tregs (*95*). Research also indicates that QUE can enhance the survival of MDSCs and stimulate the secretion of T cell inhibitory factors *in vitro*, thereby negatively regulating immune responses (*96*). Additionally, the Bushen Antai recipe has been shown to mobilize MDSCs in miscarriage-prone mice, enhancing immune tolerance and angiogenesis at the maternal-fetal interface, thereby alleviating miscarriage-related issues (*97*).

8.2. Decidual stromal cells (DSCs)

DSCs are a significant component of the decidua at the maternal-fetal interface, playing a crucial role in immune regulation through the secretion of various cytokines (*98*). Compared to patients with normal pregnancies, DSCs in RPL patients exhibit accelerated senescence, increased oxidative stress, and inhibited proliferation (*99*). The timely clearance of senescent DSCs is essential for maintaining immune balance at the maternal-fetal interface, as the accumulation of these cells may trigger inflammatory responses and propagate senescence signals, potentially leading to recurrent miscarriage (*100*). Studies have shown that QUE reduces the expression of senescence-associated beta-galactosidase-positive cells and senescence markers in DSCs, thereby facilitating the proper progression of decidualization (*101*). Furthermore, QUE partly regulates the expression of Bcl-2/Bax proteins, inhibiting apoptosis in endometrial cells, which supports successful embryo implantation (*102*). Interestingly, QUE can also activate p53, promoting apoptosis in stromal cells exhibiting a senescent-like phenotype (*103*). However, some studies in rats have indicated that subcutaneous administration of QUE at a dose of 50 mg/kg/day during the peri-implantation period may negatively impact uterine fluid volume and the development of receptivity, thereby potentially impairing embryo implantation (*104*).

8.3. Decidual extravillous trophoblast cells

DSCs regulate the function of extravillous trophoblast cells through various factors (*105*). Extravillous embryonic trophoblast cells play a vital role at the maternal-fetal interface by facilitating embryo anchoring to the maternal decidua, vascular remodeling, and immune modulation (*106*). Insufficient proliferation and invasion of extravillous trophoblast cells into the endometrium are major defects associated with pregnancy complications such as recurrent miscarriage (*107*).

Research has demonstrated that under hypoxia/reoxygenation (H/R) conditions, human trophoblast cell line HTR-8/SVneo experiences oxidative stress, accompanied by a reduction in glutathione levels and a significant decline in trophoblast invasiveness. The addition of QUE notably reduces oxidative stress, inhibits the activation of pro-apoptotic kinases induced by phosphorylation during H/R, and enhances spheroid stem cell formation in HTR-8/SVneo cells, promoting their invasive capacity (*108*). Besides, the pretreatment with QUE has been shown to prevent H/R-induced oxidative stress in trophoblast cell lines (*109*). Oxidative stress induced by placental hypoxia is closely linked to mitochondrial metabolic dysfunction, and QUE can improve mitochondrial function under hypoxic conditions, thereby promoting trophoblast cell fusion (*110,111*).

9. Conclusion

In conclusion, RPL is a common complication of clinical pregnancy with a complex etiology, often involving multiple causative factors. As a natural antioxidant and anti-inflammatory flavonol, QUE is widely found in herbal medicines, fruits, and vegetables. Current literature suggests that QUE may have therapeutic effects on RPL by regulating endocrine, coagulation, oxidation, inflammation, immune responses, and maternal-fetal interface. However, the specific molecular mechanisms of QUE remain unclear. For instance, while various studies on cellular and animal models have demonstrated the anti-inflammatory properties of QUE, an RCT observed no significant impact of QUE supplementation on innate immune function or inflammatory markers. Thus, further validation is required to determine whether QUE mitigates RPL by inhibiting the suppression of inflammation. Similarly, although QUE has been shown to regulate gut microbiota balance, the primary microbiota influenced by QUE does not align with the significant microbial alterations observed in RPL patients. This raises the question of whether QUE affects RPL by modulating gut microbiota, warranting further investigation. Additionally, while QUE can promote the clearance of senescent stromal cells and facilitate decidualization, other studies suggest that subcutaneous injection of QUE during the peri-implantation period may negatively impact embryo implantation. This highlights the need to consider the timing of QUE administration when treating RPL carefully. Due to pharmacokinetic differences, QUE's efficacy in animal models may not translate directly to humans. Dose optimization and placental barrier penetration require further exploration. To confirm the precise role of QUE in the treatment of RPL patients, more extensive and high-quality prospective trials are needed, particularly those focusing on the effects of QUE on endocrine, coagulation, oxidation, inflammation, immune response, and maternal-fetal interface-related reproductive

abnormalities. In the future, more clinical trials will likely explore the application of QUE in RPL patients.

Funding: This work was supported by a grant from the National Natural Science Foundation of China (grant No. 82374243 to L Wang) and the Chinese Association of Integration of Traditional and Western Medicine special foundation for Obstetrics and Gynecology (grant No. FCK-ZSYTW-04 to Q Qi).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received June 6, 2025; Revised June 25, 2025; Accepted June 28, 2025.

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Released online in J-STAGE as advance publication June 29, 2025.