SPANDIDOS PUBLICATIONS

WORLD ACADEMY OF SCIENCES JOURNAL 6: 10, 2024

Promising benefit of resveratrol in preventing preterm birth: A systematic review

MUHAMMAD HABIBURRAHMAN[1-3],
MUHAMMAD ILHAM DHIYA RAKASIWI[1,2] and AFID BRILLIANA PUTRA[1,2]

[1]Faculty of Medicine, Universitas Indonesia; [2]Dr. Cipto Mangunkusumo Hospital, Central Jakarta, DKI Jakarta 10430, Indonesia; [3]Faculty of Medicine, Imperial College London, London SW7 2BX, UK

Received October 2, 2023; Accepted January 5, 2024

DOI: 10.3892/wasj.2024.225

Abstract. Prematurity is a matter of utmost concern in pregnancies due to its associated complications, mortality, disability and significant economic burden. However, the current tocolytics used for preventing preterm birth have limitations, such as side-effects and unclear inhibitory pathway mechanisms. Hence, it is critical to explore alternative tocolytics, such as resveratrol. The present study, by performing a systematic review, aimed to investigate the potential of resveratrol in preventing prematurity and its therapeutic applications. A systematic search of the relevant literature was conducted using advanced search engines (PubMed, ProQuest, EBSCOhost and EMBASE), employing specific key words and predefined eligibility criteria to identify supporting articles, which were subsequently synthesized into the systematic review. Of note, four critical lines of evidence, supported by multiple studies, highlight the promising benefits of resveratrol in preventing preterm birth. In a mouse model of preterm birth, resveratrol has demonstrated the ability to: i) Reduce prematurity rates by 49-64%; ii) inhibit inflammatory mediators and cytokines (nitric oxide synthase, inducible nitric oxide synthase, cyclooxygenase (COX)-2 in the uterus, TNF-α, IL-1β, COX-2 in peritoneal macrophages and the cervixs; iii) decrease prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) levels in the uterus; and iv) regulate endocannabinoids (anandamide and 2-arachidonoylglycerol) and endocannabinoid-like lipids. By reducing the levels of these substances, resveratrol has the potential to prevent cervical ripening, membrane rupture and myometrial contractility associated with preterm birth. In summary, resveratrol offers multiple pathways to inhibit inflammation-induced prematurity, rendering it a promising candidate as a novel tocolytic agent.

Correspondence to: Dr Muhammad Habiburrahman, Faculty of Medicine, Universitas Indonesia, 6 Salemba Raya Street, Central Jakarta, DKI Jakarta 10430, Indonesia
E-mail: muhammad.habiburrahman51@ui.ac.id

Key words: anti-inflammatory effect, herbal medicine, preterm birth, resveratrol, tocolytic

Introduction

Prematurity, defined as live birth before 37 weeks of gestation by the World Health Organization (WHO), poses a global health challenge (1). In 2020, there were 13.4 million cases of preterm birth (PTB), with approximately one million resulting in mortality, as reported by the United Nations (UN). These numbers indicate that 1 in 10 babies worldwide are born prematurely (2). The number of PTBs has not improved over the last decade, with 152 million PTBs occurring from 2010 to 2020. The majority of PTBs have occurred in sub-Saharan Africa and Southern Asia, accounting for >65% of the cases globally (2). Worldwide, there has been a 5.26% reduction in newborns born prematurely, decreasing from 16.06 million in 1990 to 15.22 million in 2019. Furthermore, deaths among these newborns have significantly decreased by 47.71%, decreasing from 1.27 million in 1990 to 0.66 million in 2019 (3). Prematurity exposes infants to various health risks, such as neurocognitive deficits, pulmonary issues, heart rate irregularities, eye disorders, cerebral palsy, anemia, neonatal sepsis and intraventricular hemorrhage (4).

PTB not only has significant medical implications, but also poses substantial economic and social challenges for families. In a study conducted in the USA, researchers examined the healthcare costs associated with preterm and low-birth-weight (LBW) infants (5). That study was a retrospective cohort study using a national claims database of individuals covered by Aetna, Inc. during the first 6 months of life. The study included a total of 763,566 infants with a combined healthcare expense of approximately $8.4 billion. Preterm infants (n=50,511) had an average medical cost of $76,153, while LBW infants had an average cost of $114,437. Among infants born at 24 weeks of gestation (n=418), the average cost per infant was the highest at $603,778 (5).

The pathophysiology of PTB involves various factors, such as genetics, infection/inflammation, environment, oxidative stress, progesterone resistance and an advanced maternal age (6). Infection-related inflammation is the primary cause, accounting for 40% of cases (7). Experimental mouse models are crucial for studying the mechanisms and potential therapies for prematurity. Maternal inflammation in these models is induced using bacterial lipopolysaccharide (LPS) endotoxin, which triggers the release of cytokines, the

infiltration of leukocytes and the production of cyclooxygenase (COX)-induced prostaglandins (PGs), endocannabinoids, reactive oxygen and nitrogen species (RONS) and metalloproteinases (8). This immune response leads to uterine contractions, membrane rupture and cervical ripening (9). Mice with a genetic predisposition to PTB (e.g., *Trp53* deficiency) also exhibit inflammation when exposed to LPS. These models provide valuable tools for evaluating novel treatments for the challenges associated with PTB (10,11).

The clinical management of preterm labor is challenging as no single drug effectively addresses all its mechanisms. Current therapeutics involve the use of tocolytics, which delay preterm labor and enable the administration of corticosteroids for neonatal lung maturation (12). Tocolytics include magnesium sulfate, β-mimetics, calcium channel blockers, PG inhibitors and oxytocin receptor antagonists (13). However, these drugs have limitations and potential side-effects, and there is insufficient evidence for significant neonatal benefits (14). Existing tocolytics also have limitations and lack strong evidence for maternal or neonatal outcomes (15,16). Consequently, efforts are underway to discover novel tocolytic agents that are more effective and safer. One such promising candidate is resveratrol.

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural polyphenol known for its beneficial effects on inducing preterm labor (11,17) and other pregnancy-related complications (18,19). It exhibits anti-inflammatory and anti-aging properties, rendering it a potential therapeutic target for PTB (8,17). However, there is a lack of comprehensive studies on the specific benefits of resveratrol in preventing prematurity. Therefore, the present systematic review aimed to explore the potential of resveratrol in preventing prematurity, including its pharmacological profile, content in various plant species and therapeutic applications.

Data and methods

Protocol. The present descriptive qualitative systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (20).

Information sources and search strategy. The search, conducted in July-August 2023, aimed to identify studies on the mechanisms of resveratrol in preventing PTB in animal models. The present systematic review followed the PICOS format: Population (P)-Pregnancy with induced PTB; Intervention (I)-Resveratrol; Comparison (C)-Negative control (untreated with resveratrol); Outcome (O)-Prevention of PTB (tocolytic effect); Study Design (S)-Preclinical studies. Specific search strategies were used for various databases, including MEDLINE via PubMed, ProQuest, EBSCOhost and EMBASE. The search queries and MESH keywords combined with Boolean operators were used, such as 'Resveratrol' (Mesh) AND ['Premature Birth' (Mesh) OR 'Obstetric Labor, Premature' (Mesh)].

Study selection and data collection process. The studies were selected based on the eligibility criteria using the PICOS strategy. The inclusion criteria were as follows: i) English-language articles; ii) primary experimental studies utilizing resveratrol (*in vitro* and *in vivo*); and iii) outcomes related to PTB. The exclusion criteria encompassed the following: i) Duplicated articles; ii) abstracts and reviews lacking specific data; iii) clinical studies, systematic reviews, case reports, retrospective studies, theses, letters, editorials, opinions, surveys, guidelines, conferences, abstracts and commentary articles. Initially, a search was performed for human population studies; however, as none were found, a focus was placed solely on reviewing experimental animal studies. Articles focusing solely on the benefits of resveratrol for preterm infants after birth were also excluded. In total, the authors (MH, MIDR and ABP) independently screened titles and abstracts, removing duplicates. Eligible articles had their full texts examined for confirmation. No restrictions on publication dates were applied to the systematic review. The search process is illustrated in Fig. 1.

Quality assessment and risk of bias. To assess the quality of the studies, the ToxRTool (Toxicological Data Reliability Assessment Tool), developed by ECVAM (European Centre for the Validation of Alternative Methods) (21) was used. This tool provides criteria for evaluating the quality of pharmacology research using *in vitro* and *in vivo* experimental study designs. Previous systematic reviews that utilized the ToxRTool were also considered to determine the methodological reliability and inherent flaws in the studies (22-24). The ToxRTool consists of a 21-point rating checklist that assesses the methodological aspects of each study across five categories (25). These categories cover various aspects, including Category 1 (test substance identification), which includes details about (1.1) the substance, (1.2) purity, (1.3) source, and (1.4) nature and physico-chemical properties; Category 2 (test organism characterization), which includes (2.1) species (for *in vivo* studies) or test system (for *in vitro* studies), (2.2) sex (for *in vivo* studies) or the origin or source of the test system with the corresponding sex characteristic (for *in vitro* studies), (2.3) strain of test animals (for *in vivo* studies) or the specification of cell/tissue culture (for *in vitro* studies), (2.4) age or body weight of test organisms at the start of the study (for *in vivo* studies) or relevant clinical characteristics of human donors for cell/tissue cultivation (for *in vitro* studies), and (2.5) housing or feeding conditions in repeated dose studies (for *in vivo* studies) or cultivation process maintenance (for *in vitro* studies); Category 3 (study design description), which includes (3.1) administration method, (3.2) administered doses or concentration in the application media, (3.3) exposure frequency, duration, and explanation of observation time-points, (3.4) inclusion of negative and positive controls, (3.5) the number of animals (for *in vivo* studies) or the amount of cell/tissue culture per group (for *in vitro* studies), (3.6) administration scheme details for study evaluation, and (3.7) verification of achieved concentrations or substance stability in repeated dose studies; Category 4 (study endpoints), which includes (4.1) clear description and determination methods of endpoints, (4.2) transparent and comprehensive results description for all endpoints, and (4.3) transparent statistical methods for data analysis; and Category 5 (study design appropriateness and reliability), which includes (5.1) appropriate choice of study design for substance-specific data and (5.2) reliability of quantitative results. Studies with <13 points are deemed

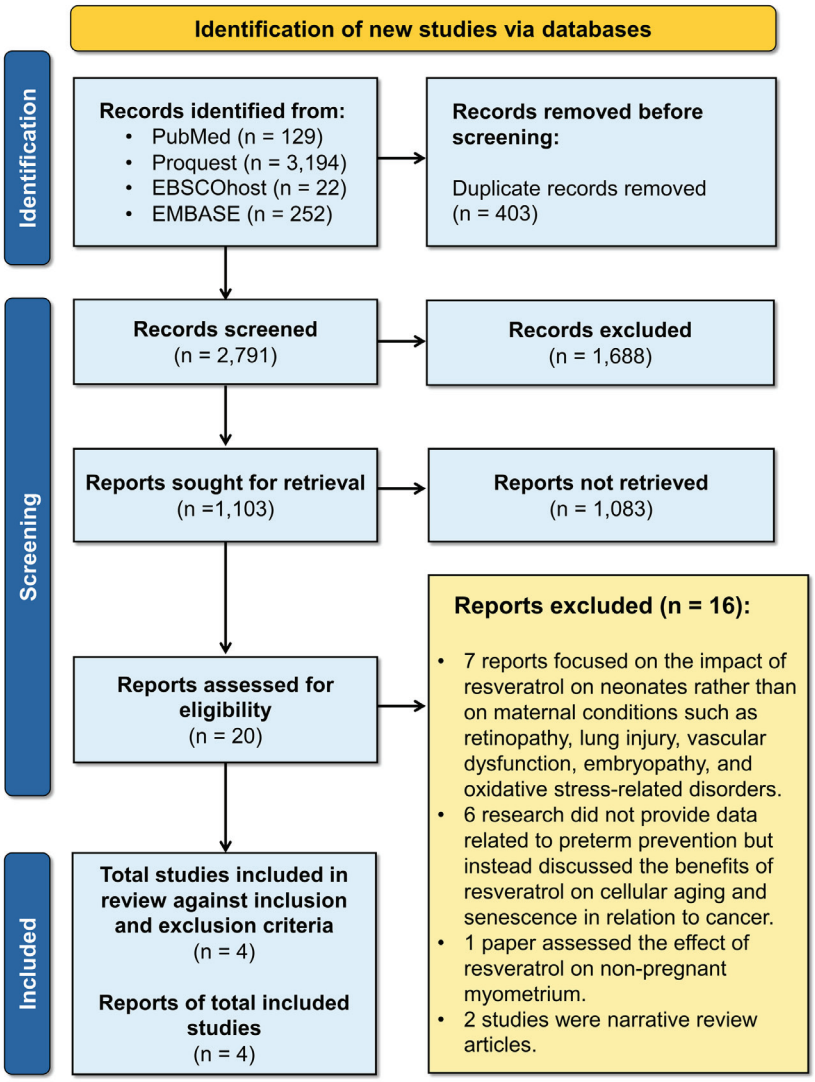

Figure 1. Flowchart depicting the article selection process based on the PRISMA 2020 guidelines for conducting a systematic review.

unreliable, those with 13-17 points are considered reliable with potential restrictions, and those scoring 18-21 points are deemed reliable without restrictions.

In addition, a risk of bias (RoB) assessment tool based on the Cochrane Handbook (26) was used with modifications that integrated the Office of Health Assessment and Translation, National Institute of Health (OHAT-NIH), and the National Toxicological Program tools, as used in previous studies (27-29). Three authors independently assessed all included studies for bias risk across nine parameters (randomization, allocation concealment, experimental conditions, blinding during the study, data completeness, exposure characterization, outcome assessment, selective reporting and data sufficiency). The responses were categorized as low risk (yes, provided information), unclear risk, or high risk (no, absent information) of bias following predefined protocol criteria. Any disagreements, conflicts, or discrepancies regarding the eligibility of studies were resolved through discussion and consensus to determine inclusion.

Data extraction. Data extraction was performed using Microsoft Office Excel 365. Three reviewers independently organized the data into variables based on the review's aims and topics. These variables included publication year, author(s), first author's country, study design, level of evidence (LoE) according to the Oxford Centre of Evidence-based Medicine (CEBM) criteria (30), preterm model sample, sample size, induced diseases and definitions. The outcomes data included the dose of resveratrol and administration details, treatment duration and frequency, additional drugs used, and associated study outcomes.

Synthesis of results. The relevant data of interest regarding the aforementioned variables were collected and organized into summary tables for study characteristics and outcomes using an electronic spreadsheet. The studies were further grouped based on similarities in reducing preterm rates and common underlying mechanisms.

Results

Study selection. The PRISMA flow diagram was followed for allocation concealment, blinding, article review, and data extraction. Initially, 3,597 results were retrieved from all

Table I. Reliability assessment of the selected articles according to the ToxRTool *in vivo* and *in vitro* criteria.

	Studies included in the systematic review [Authors/(Refs.), year of publication			
Reliability of study assessment	Bariani *et al* (8), 2017	Deng *et al* (11), 2016	Furuya *et al* (17), 2015	Novaković *et al* (31), 2015
Criteria I: Test substance identification (maximum point 4)	4	2	4	4
Criteria II: Test organism characterization (maximum point 5)	4	3	3	4
Criteria III: Study design description (maximum point 7)	5	4	5	5
Criteria IV: Study results documentation (maximum point 3)	3	3	3	3
Criteria V: Plausibility of study design and data (maximum point 2)	2	1	2	2
Total score	18	13	17	18
Reliability classification	Reliable without restrictions	Reliable with restrictions	Reliable with restrictions	Reliable without restrictions

The scoring system was as follows: 18-21, reliable without restrictions, and thus being useful for the intended purpose; 13-17, reliable with restrictions, and thus being potentially useful for the intended purpose; <13 or not all critical criteria met, generally not to be used as a crucial study, but depending on the shortcomings of the study, it may still be helpful in weight-of-evidence approaches or as supportive information.

databases, which were reduced to 2,791 after removing duplicates. Screening based on titles and abstracts resulted in 1,103 articles, and after applying inclusion and exclusion criteria, 20 full-text articles were assessed for eligibility. Ultimately, only four articles were eligible for analysis and review. Additionally, searches were conducted on Google Scholar and various Gray Literature websites (http://www.opengrey.eu/search/, https://v2.sherpa.ac.uk/opendoar/, https://www.worldcat.org/, and https://ukhsalibrary.koha-ptfs.co.uk/greylit/). However, no additional results were obtained beyond those included in the initial selection from the central journal databases.

Study exclusion. A full-text assessment was conducted after removing all duplicate references using Zotero version 6.0.26 as the reference manager. The exclusion criteria included studies that focused on the effects of resveratrol on neonates as opposed to maternal conditions, such as retinopathy, lung injury, vascular dysfunction, embryopathy and oxidative stress-related disorders (n=7). Studies that discussed the benefits of resveratrol for cellular aging and senescence in cancer were also excluded (n=6). Additionally, a study that assessed the effects of resveratrol on non-pregnant myometrium was excluded (n=1), as well as narrative reviews (n=2).

Reliability and quality assessment. As regards the reliability assessment (Table I), two studies [Bariani *et al* (8) and Novaković *et al* (31)] were deemed fully reliable and were included in the systematic review. However, two other studies [Deng *et al* (11) and Furuya *et al* (17)] were labeled as 'reliable with restrictions' due to methodological uncertainties and the absence of critical quality measurement categories. Specifically, the study by Deng *et al* (11) lacked information on the purity and origin of resveratrol, the age and other characteristics of the mice used, the environmental conditions for the mice, positive controls, a precise number of samples, and details on the stabilization and extraction/obtaining of resveratrol. Similarly, the study by Furuya *et al* (17) had limitations in sample characteristics and conditioning during the experiment, as well as a lack of a positive control and information on the stabilization of resveratrol. Detailed assessments for each category are provided in Tables SI-SIII.

In the risk of bias summary (Fig. 2), Bariani *et al* (8) had a low risk of bias in seven out of nine domains in each RoB category, with two aspects rated as high risk. Novaković *et al* (31) had a low risk of bias in five of nine domains in each RoB category, with one aspect considered unclear risk and the remaining three as high risk. Deng *et al* (11) and Furuya *et al* (17) each demonstrated a low risk of bias in three domains, an unclear risk in three other domains, and three domains with high risk. Despite all the limitations in the reliability and quality assessment, all studies were eligible to be assessed and reviewed in the present systematic review. According to the CEBM levels, they all fall under the fifth level of EBM (1 to 5).

Study design and outcomes measurement. The present systematic review included two experimental *in vivo* studies [Bariani *et al* (8) and Furuya *et al* (17)] and one study combining animal and cell experiments [Deng *et al* (11)]. All these studies investigated the effect of resveratrol on preventing PTB in animal models. Additionally, one *in vitro* study [Novaković *et al* 2015 (31)] focused on the tocolytic and myometrium relaxant effects of resveratrol using human myometrium tissue to determine the preterm mechanisms. In this section, several studies that examined the preventive effects of resveratrol on PTB are presented. These studies

A

No.	Studies	Randomisation	Allocation concealment	Experimental condition	Blinding during study	Data completeness	Exposure characterization	Outcome assessment	Reporting	Sufficiency data
1	Bariani *et al*, 2017	+	–	+	–	+	+	+	+	+
2	Deng *et al*, 2016	–	–	?	–	+	+	+	?	?
3	Furuya *et al*, 2015	–	–	?	–	+	+	+	?	?
4	Novakovic *et al*, 2015	–	–	+	–	+	+	+	+	?

Colouring code for the categories:

- Definitely low risk of bias
- Probably low risk of bias or unclear risk of bias
- High risk of bias

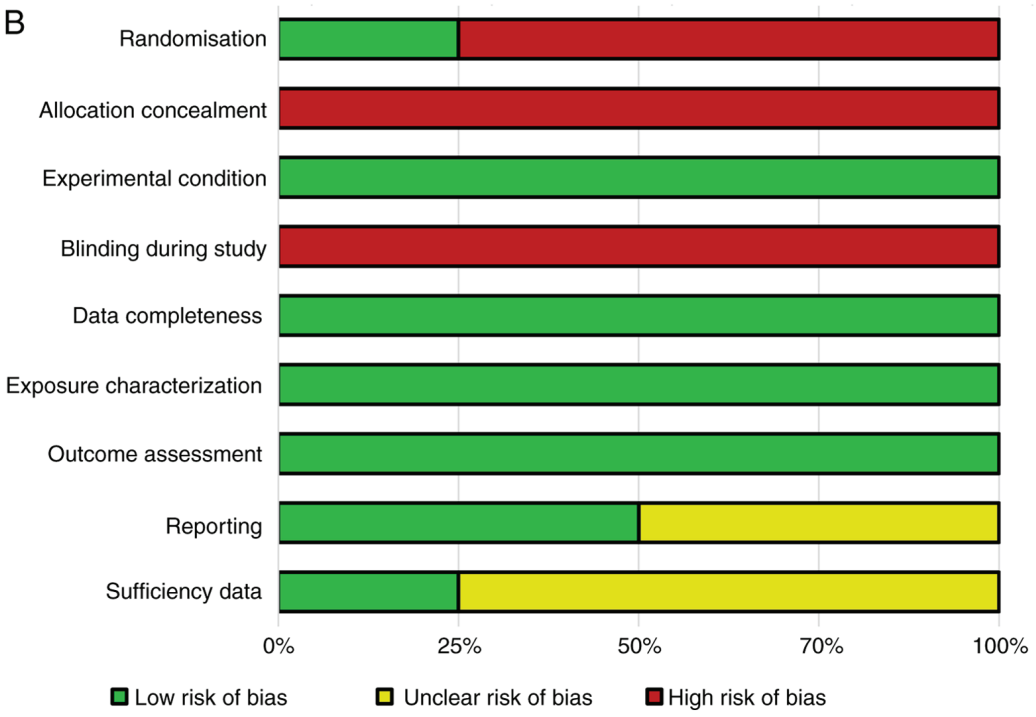

Figure 2. Summary of the quality assessment of the studies included in this systematic review: (A) The authors assessed the risk of bias for each study and presented the results in a tabular format using various symbols (a green round shape with a plus sign indicates a low risk of bias, a yellow round shape with a question mark represents an unknown or unclear risk of bias, and a red round shape with a hyphen indicates a high risk of bias). This assessment followed the guidelines provided by the Office of Health Assessment and Translation, the National Institute of Health (OHAT-NIH), and the National Toxicological Program. (B) Comprehensive summary of the risk of bias across the studies.

include information about its characteristics (Table II), as well as its beneficial preventive effects on PTB (Table III).

Discussion

Complications arising from PTB are a major contributor to neonatal mortality and the second leading cause of mortality among children under the age of 5 years. Surviving children often experience lifelong disabilities. The reduction of PTB rates is a global priority, due to its significant impact on healthcare and the economy (5). Addressing prematurity continues to be a significant challenge in the field of maternal and child health, as there is no single drug that effectively targets all the underlying pathways leading to prematurity. Each tocolytic agent has its own limitations and potential side-effects, with limited evidence of efficacy in improving neonatal outcomes (32).

The present systematic review examined four articles that explored the role of resveratrol in cases of prematurity. The studies were conducted between 2015 and 2017, with two taking place in developing countries (Argentina and Serbia) (8,31) and the other two in developed countries (USA and Japan) (11,17). The analysis included two *in vivo* studies conducted on mice (8,17), one *in vitro* study using human myometrial tissue (31), and one study that combined both *in vivo* and *in vitro* research (11). In the *in vivo* studies, PTB was induced using LPS, and resveratrol was administered orally (8,11,17). However, the dosage and timing of resveratrol varied, ranging from 3 to 40 mg/kg on days 8 to 15. In the *in vitro* studies, resveratrol was applied as a bath to cell tissue that had been previously exposed to oxytocin (11,31). To the best of our knowledge, there is no published study available on the potential impact of resveratrol dosages on human tissues and cells. However, the available studies have indicated that when resveratrol is orally administered to mice, the compound remains unaltered and is retained within the tissues (33).

Following oral administration, low concentrations of resveratrol have been detected in both the plasma and tissues of humans and experimental animals (34). Studies that involved the incremental dosing of resveratrol from 25 to 5,000 mg consistently demonstrated an increase in plasma concentrations without any signs of metabolic saturation. However, even at the highest dose of 5,000 mg, the observed peak plasma levels only reached ~500 ng/ml. There is a possibility of metabolic saturation with prolonged or repeated dosing, which may result in elevated resveratrol levels in plasma and tissues (35). Although it remains a hypothesis, studies have suggested that it may be possible to achieve biologically active concentrations of resveratrol and/or its metabolites in human subjects through chronic dosing (36,37).

Bariani *et al* (8) and Furuya *et al* (17) demonstrated that resveratrol effectively reduced the incidence of PTB in mice through the reduction of pro-inflammatory cytokines (e.g., TNF-α and IL-1β). Novaković *et al* (31) demonstrated that resveratrol significantly decreased both rhythmic contractions and contraction amplitude. However, Deng *et al* (11) argued that resveratrol alone may not be sufficient in preventing PTB events. By analyzing these four articles alongside supporting literature, the authors compiled a comprehensive understanding of the risk factors and pathophysiology of prematurity. Additionally, the present study explored the mechanisms of action through which resveratrol targets prematurity mechanisms, the efficacy of resveratrol as a preventive agent for PTB, and the pharmacological characteristics of resveratrol, from experimental settings to clinical applications.

Pathophysiology of prematurity in cellular and animal studies. The limited understanding of the complex etiology of PTB is a barrier to the development of effective strategies for its prevention. Recognized risk factors for PTB include multiple pregnancies, chorioamnionitis, maternal diseases, genetic factors, previous PTB and uterine abnormalities. However, not all cases of PTB have identifiable risk factors. The pathophysiology of PTB involves various processes, including myometrial contraction and extracellular matrix degradation. Among these processes, inflammation, which is initiated following implantation, plays a crucial role in PTB (37,38). Experimental animals, primarily mice or rats, play a critical role in studying the pathophysiology of PTB. The commonly used inflammation-inducing agent is LPS, derived from *Escherichia coli* endotoxins, administered intrauterine or intraperitoneally (39). In addition to LPS, various methods, including hormonal or immune agents, can induce PTB in mice (39).

Immunity, both innate and adaptive, plays a crucial role in the incidence of PTB. In mouse studies, macrophages induce PTB by producing pro-inflammatory cytokines such as matrix metallopeptidases, IL-1, IL-6 and IL-8. In the mouse model, PTB can be prevented by inhibiting the IL-1 receptor via the NF-κβ pathway (40). IL6-deficient mice exhibit resistance to LPS-induced PTB (41). Complement activation is also significant in preventing PTB, as women with spontaneous preterm labor have increased levels of complement C3a, C4a and C5a in infection-associated cases. Mice lacking the C5aR complement receptor demonstrate resistance to LPS-induced PTB *in vitro* (42).

In addition to the role of the innate immune system in PTB, the adaptive immune response is significant. PTB often occurs due to maternal intolerance to fetal antigens. Regulatory T-cells (Tregs) and effector T-cells (Teffs) undergo changes in frequency and phenotype. Tregs in women in preterm labor exhibit differential activation and reduced suppressive capacity (6). Toll-like receptors (TLRs) are another crucial component of the immune response. They activate signaling pathways that lead to cytokine and chemokine secretion by innate immune cells. TLR activation initiates inflammatory pathways that result in vaginal and preterm labor, immune cell recruitment, PG and MMP production, cervical ripening, and uterine contractions. TLR4 and TLR2 influence the timing of delivery during pregnancy (43,44). In addition to maternal TLR expression, fetal TLR expression may impact birth timing, with polymorphic alleles of fetal TLR4 and TLR2 associated with prematurity (45).

Current research explores the role of the microbiome role in modulating the risk of PTB. The composition of the vaginal microbiota influences the risk of PTB, with dysbiosis linked to increased levels of pro-inflammatory cytokines, such as CXCL10, in early pregnancy (46). However, administering pre-conception antibiotics to women with a history of PTB does not reduce the rates of PTB; instead, it is associated with a lower occurrence of LBW babies and early labor (47).

Table II. Characterization of the articles included in the systematic review.

Authors, year of publication	Region	Study Design	LoE	Sample	Sample size	Preterm induction model	Disease induction and operational definition	(Refs.)
Bariani *et al*, 2017	Argentina	*In vivo*	5	15-days pregnant BALB/c mice	±35-41 mice	Inflammatory induction: LPS i.p. (0.17 mg/kg and 0.5 mg/kg after 3 h) on day 15	• LPS-induced preterm labor • Preterm labor was defined as labor occurring 19 days	(8)
Deng *et al*, 2016	USA	*In vivo* and *in vitro*	5	• *Trp53*$^{fl/fl}$ *Pgr*$^{Cre/+}$ mice (*p53*$^{d/d}$ mice) and floxed *p53* mice (*p53*$^{fl/fl}$), which are genetically predisposed to PTB • Human uterine fibroblast (HuF) cells, which were decidualized *in vitro* and placenta obtained from term and preterm (at 23 weeks) vaginal delivery. • *p53*$^{fl/fl}$ and *p53*$^{d/d}$ uterine stromal cells, which were decidualized *in vitro* obtained from 4-days pregnant mice • Mouse embryonic fibroblasts (MEFs) from *Prkaa1*$^{-/-}$ *Prkaa2*$^{-/-}$ double knockout (AMPK dKO), WT, and *p53*$^{-/}$ mice	• The exact number of mice was not mentioned • Samples from 3 women were used for human cell studies	• *In vivo* model: conditional uterine deletion of the tumor suppressor gene *p53* • Superimposed inflammatory insult: LPS (10 μg) administered 4 h following a progesterone injection (1-2 mg/mouse) on day 16 • *In vitro* model: Hormone treatment to induce decidualization in cultured uterine stromal cells	• Spontaneous PTB in *p53*$^{d/d}$ females, both with and without dystocia • Preterm labor was defined as labor occurring before 19 days • Dystocia was defined as a problematic delivery lasting >12 h	(11)
Furuya *et al*, 2015	Japan	*In vivo*	5	7-days pregnant C57BL6 mice	12 mice	Inflammatory induction: Transvaginal administration of LPS (10 μg in 200 ml saline) to the cervix and uterus on day 15	• LPS-induced preterm labor • Preterm labor was defined as labor occurring before 19 days. • PTB occurred within 48 h	(17)
Novaković *et al*, 2015	Serbia	*In vitro*	5	Myometrial samples were obtained from females undergoing an IVF program and currently scheduled for elective C-section (due to cephalopelvic disproportion) in the third trimester of pregnancy. Biopsies were excised from the mid-line portion of the upper lip of the incision in the lower uterine segment	Myometrial tissue samples were collected from 42 non-laboring women	Contraction inducer: Oxytocin (20 nM)	• Oxytocin-induced phasic contractions of constant amplitude and frequency in human-term pregnant myometrium • This study did not specifically focus on preterm labor, but the outcomes are still relevant in the context of tocolytic research	(31)

AE, N-acyl ethanolamine; AMPK, AMP-activated protein kinase; C-section, cesarean section; CPD, cephalopelvic disproportion; HuF, human uterine fibroblast; IVF, *in vitro* fertilization; LoE, level of evidence; LPS, lipopolysaccharide; MEF, mouse embryonic fibroblasts; mg, milligram; ml, milliliter; nM, nanomolar; PTB, preterm birth; WT, wild type; μg, microgram.

Table III. Summary of the articles analyzed in the systematic review focusing on the effect and potential benefit of resveratrol in preventing preterm birth.

Authors, year of publication	Resveratrol dose and route	Duration frequency	Additional drug	Outcomes	(Refs.)
Bariani *et al*, 2017	3 mg/kg, PO	On day 15, per 8 h	N/A	• Resveratrol reduced the proportion of PTB compared to the control group (64% vs. 85%) • Resveratrol reduced stillbirth compared to the negative control group (stillbirth, 34 vs. 62%) • Resveratrol prevented antepartum hemorrhage based on macroscopic examination. • Resveratrol may protect against pathological PTB by reducing uterine NOS activity, the expression of iNOS, COX-2, PGE2, and AEA profiling (P<0.05) • Resveratrol altered the uterine endocannabinoid profiling that was previously affected by LPS	(8)
Deng *et al*, 2016	30 mg/kg PO	On days 8,10,12 and 14	• A single injection of progesterone (1-2 mg/mouse) was administered 4 h before LPS induction • Metformin 1 mg/kg was administered on days 8, 10 and 12 separately (not combined with resveratrol)	• The combination of resveratrol + progesterone is an effective approach for targeting both decidual health and compensating ovarian luteolysis • Resveratrol or progesterone alone could not prevent the incidence of PTB and did not increase the number of live mouse pups • Resveratrol reduced PGE2 levels with limited effects on PGF2α levels in both *p53*$^{fl/fl}$ and *p53*$^{d/d}$ decidual cells, as indicated by lower expression of *Ptgs2* (encoding COX2) in mice and human decidual cells treated with resveratrol • Resveratrol has an inverse regulatory effect on AMPK and mTORC1 signaling in decidual cells, controlling parturition timing to prevent PTB • Resveratrol did not appear to have detrimental effects on pregnancy outcomes • Progesterone injection alone showed some adverse effects on pup viability, likely due to the normal decline in progesterone levels approaching parturition	(11)
Furuya *et al*, 2015	20 and 40 mg/kg PO	On days 12-14 1x/day; On day 15 2x/day (at 6 to 12 h after LPS injection)	N/A	• Resveratrol decreased the rate of PTB compared to the control group (48.6±19.4 vs. 97.8±1.9%) • Resveratrol may protect against pathological PTB by suppressing the elevated levels of pro-inflammatory cytokines TNF-α (16.7 vs. 53.9 pg/ml) and IL-1β (88.4 vs. 403 pg/ml), but not IL-6 levels in peritoneal washes • Resveratrol inhibited mRNA expression of TNF-α in uterine cervices, but not IL-1β and IL-6 levels • Resveratrol dose-dependently reduced mRNA expression of TNF-α and IL-1β, but not IL-6 levels, in peritoneal macrophages • Resveratrol suppressed the pro-inflammatory cytokine-mediated elevation of COX-2 mRNA levels produced by peritoneal macrophages	(17)
Novaković *et al*, 2015	A range between	Resveratrol was incrementally	• Glibenclamide (10 μM)	• Resveratrol with the concentration of 1-100 μM might inhibit the amplitude of oxytocin-induced contractions in a concentration-dependent manner (pD2 4.52+0.11,	(31)

Table III. Continued.

Authors, year of publication	Resveratrol dose and route	Duration frequency	Additional drug	Outcomes	(Refs.)
	1-100 μM PO	added to the bathing solution, allowing for equilibrium response to be achieved within ~20 min	• Iberiotoxin (100 nM) 4-Amino-pyridine (1 mM)	maximal responses: 82.25+1.50%) • Resveratrol significantly reduced spontaneous rhythmic contractions and the amplitude of phasic contractions induced by oxytocin but had no effect on tonic contractions induced by oxytocin • Resveratrol suppressed the contractility of human term pregnant myometrium by modulating different myometrial K^+ channels, including the activation of KATP channels, Kv channels, and BKCa channels through an increase in intracellular Ca^{2+} • Resveratrol may induce relaxation of pregnant myometrium, at least partially, through the activation of Kir6.2/SUR1 channels. Resveratrol at a concentration of 10 mM showed insensitivity to all K^+ channel blockers	(31)

AEA, N-arachidonoylethanolamine; AMPK, AMP-activated protein kinase; COX-2, cyclooxygenase 2; kg, IL, interleukin; iNOS, inducible nitric oxide synthase; Kilogram; Kv channel, Voltage-gated potassium channel; LPS, lipopolysaccharide; mg, milligram; ml, milliliter; mRNA, messenger RNA; mTORC 1, mammalian target of rapamycin complex 1; nM, nanomolar; NOS, nitric oxide synthase; pg, picogram; PGE2, prostaglandin E2; PGF2α, prostaglandin F2α; TNF-α, tumor necrosis factor α; PO, per oral; PTB, preterm birth; μM, micromolar.

Among the various mechanisms associated with PTB, including innate immunity, adaptive immunity and dysbiosis, there is a notable interest in elucidating the mechanisms through which resveratrol intervenes in these processes. Resveratrol demonstrates antimicrobial properties against various pathogenic microorganisms, encompassing both Gram-positive and Gram-negative bacteria, as well as fungi. It can inhibit the growth of specific bacterial species at concentrations below 100 μg/ml, although higher concentrations are required to inhibit the growth of many bacterial organisms (48). The mechanism of action of resveratrol involves multiple pathways. It inhibits the electron transport chain and F0F1-ATPase, resulting in reduced cellular energy production. Resveratrol also interferes with DNA through the formation of a Cu(II)-peroxide complex and suppresses cell division by targeting the FtsZ gene. Moreover, it is effective in preventing biofilm formation and acts as both an antibiofilm and an anti-quorum sensing agent (49). The additional proposed mechanisms of action of resveratrol have been succinctly outlined in Fig. 3.

Mechanisms of action: Resveratrol targeting the mechanism of prematurity

Reduction of inflammatory mediators [nitric oxide (NO) synthase (NOS) and inducible NOS (iNOS)] in the uterus. The beneficial effects of resveratrol in inflammation-induced preterm delivery involve multiple pathways. One of these pathways is the decrease in the activity of uterine NOS and the protein expression of uterine iNOS. The excessive production of NO leads to the formation of RONS, which are associated with tissue damage, oxidative and nitrative stress (50). To assess the activity of NOS and the protein expression of iNOS in the uterus, measurements were taken 5 h following the injection of LPS. The results indicated an increase in NOS and iNOS activity in mice treated with LPS alone. Bu contrast, mice treated with resveratrol after LPS exposure showed no significant increase in NOS activity (51). This reduction in uterine NOS and iNOS activity is beneficial as it prevents excessive production of NO and its associated adverse effects, such as damage to reproductive tissues and oxidative stress (51).

Reduction of levels of inflammatory cytokines (TNF-α, IL-1β and IL-6) in the cervix and peritoneum. Resveratrol is known to inhibit the activity of NF-κβ, a transcription factor involved in the expression of pro-inflammatory cytokines, in various immune response-related disease models (52). This factor operates not only in immune cells but also in the uterine myometrium, decidual stroma and amniotic cells (17). It promotes the production of cytokines, such as TNF-α, IL-1β, IL-6 and IL-8, which are crucial for inducing labor, particularly in preterm cases (53,54). Resveratrol appears to inhibit this NF-κβ/cytokine loop (17).

Furuya *et al* (17) focused on murine pro-inflammatory cytokines and observed significant increases in the levels of TNF-α, IL-1β and IL-6 in peritoneal washes and cervical tissues following exposure to LPS. In their *in vivo* model, resveratrol effectively suppressed the elevation of TNF-α and IL-1β levels induced by LPS, with a slight reduction in IL-6 levels (17). Although IL-6, produced by various stromal cells, was not as markedly suppressed, it may be due to its induction by other pro-inflammatory cytokines and direct stimulation by

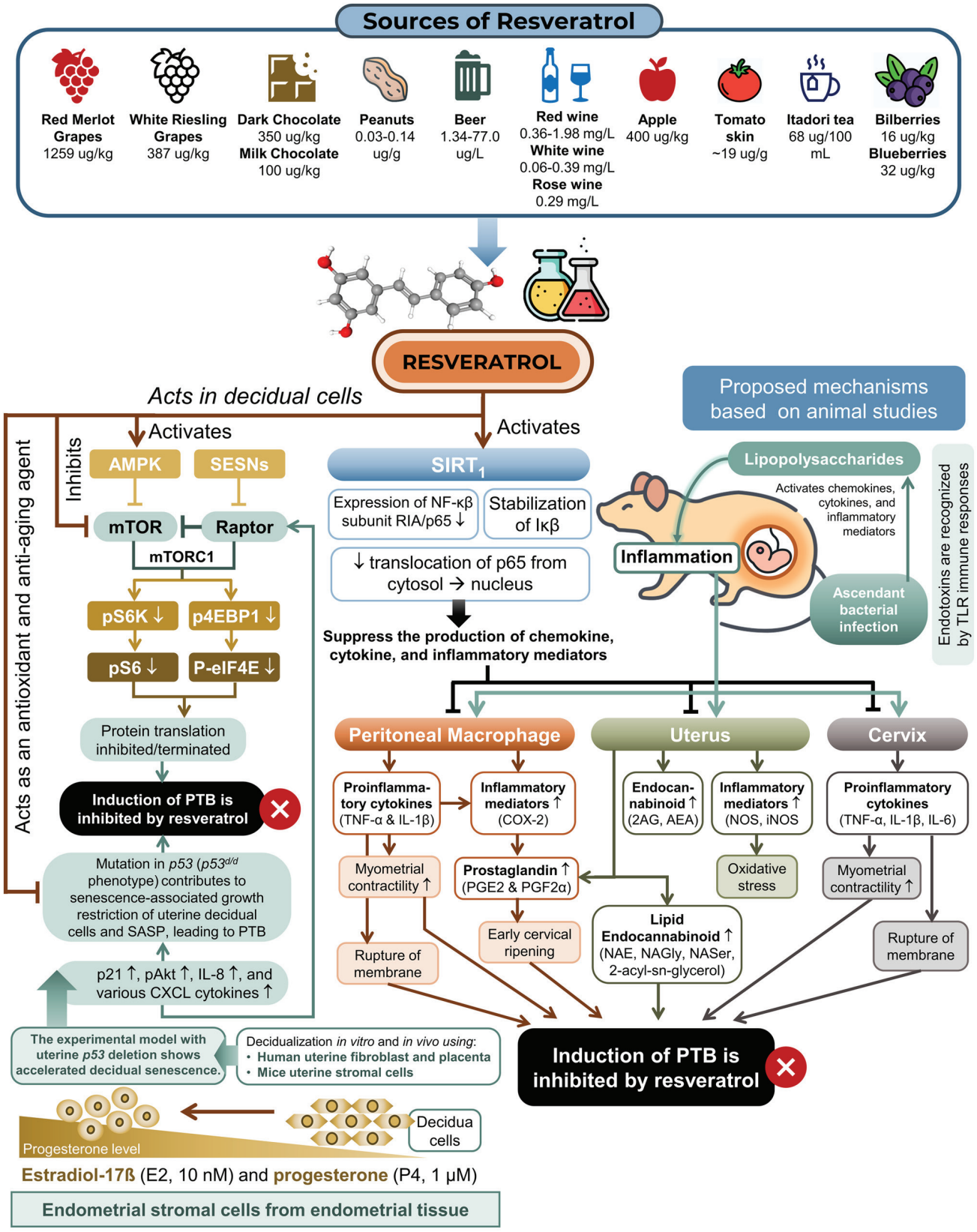

Figure 3. Proposed mechanism of action of resveratrol in preventing PTB. The mechanism involves reducing inflammatory mediators and cytokines in the uterus, cervix and peritoneum, suppressing prostaglandin production, and modulating the endocannabinoid profile. Experimental studies using a transgenic mammalian model with uterine *p53* deletion revealed accelerated decidual senescence, characterized by elevated levels of p21, p-Akt, IL-8 and various CXCL cytokines, collectively contributing to the SASP. In $p53^{d/d}$ females, this senescence-associated growth restriction of uterine decidual cells occurs, and at this stage, resveratrol functions as an antioxidant and anti-aging agent by activating AMPK and inhibiting mTORC1 signaling in decidual cells (8,11,17,31). AMPK, AMP-activated protein kinase; g, gram; IκB, IκB kinase; IL, interleukin; COX-2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; kg, kilogram; L, liter; mg, milligram; ml, milliliter; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; NAE, N-acyl ethanolamine; NAGly, N-arachidonoyl glycine; NASer, N-arachidonoyl serine; NF-κβ, nuclear factor kappa B; nM, nanomolar; NOS, nitric oxide synthase; PGE2, prostaglandin E2; PGF2α, prostaglandin F2 alpha; pAKT, phosphorylated Akt; PTB, preterm birth; SASP, senescence-associated secretory phenotype; SESNs, sestrin protein; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; μg, microgram; μM, micromolar.

LPS (55). Since the preterm delivery model is initiated by the stimulation of TLRs in macrophages by LPS, inhibiting the expression of TNF-α and IL-1β in peritoneal washes and the uterine cervix directly suppresses this signaling pathway (17).

Resveratrol effectively suppresses the production of pro-inflammatory cytokines in the cervix, which is a key factor in the pathogenesis of PTB. PTB often involves local inflammation caused by microbial infection, resulting in elevated levels of cytokines, PGs, uterine contractions, and cervical ripening (56). In the study by Furuya *et al* (17), cervical tissues exposed to LPS in the control group exhibited significantly higher mRNA levels of TNF-α, IL-1β and IL-6 compared to the group treated with resveratrol(17). Resveratrol notably reduced the peak levels of TNF-α and IL-1β mRNA, particularly resulting in significantly lower TNF-α levels (0.54±0.09) in the resveratrol-treated group compared to the control group (2.45±0.93) (17). Resveratrol also demonstrates anti-inflammatory effects on placental tissues in pregnant women by downregulating the sirtuin-1 gene post-delivery (57). Its mechanism involves inhibiting the transcription activity of NF-κB, reducing the expression of the NF-κβ sub-unit RelA/p65, and stabilizing inhibitory I-κβ (57,58). Previous studies have demonstrated that resveratrol can suppress inflammatory responses in endometrial stromal cells in patients with endometriosis. The excessive production of pro-inflammatory cytokines can further stimulate the overproduction of PG, leading to increased uterine contractions and cervical maturation (59). Therefore, the ability of resveratrol to suppress pro-inflammatory cytokines in the cervix holds promising therapeutic implications for preventing PTB.

The pathogenesis of PTB involves both the cervix and the peritoneal area. In the study by Furuya *et al* (17), the injection of LPS into the cervix significantly increased the levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in peritoneal washes, with IL-1β spiking to levels 480 times higher (17). This led to intrauterine inflammation and PTB in the experimental model. Peritoneal washes assessed the local immune responses to LPS, and the administration of resveratrol markedly decreased the levels of TNF-α and IL-1β. TNF-α levels were reduced to one-third, and IL-1β to about one-fourth, in mice treated with resveratrol compared to controls. However, there was no significant difference in IL-6 levels between the groups (17). Furuya *et al* (17) also demonstrated that resveratrol prevented the increased production of TNF-α and IL-1β by peritoneal macrophages in response to LPS. Comparing the local immune responses within 4 h of the injection, the results of peritoneal lavage revealed a significant decrease in TNF-α and IL-1β levels following the administration of resveratrol (17). TNF-α levels were approximately one-third in mice treated with resveratrol (16.7 vs. 53.9 pg/m), while IL-1β levels were approximately one-quarter (88.4 vs. 403 pg/ml, $P<0.01$). However, there was no significant difference in IL-6 levels between the resveratrol-treated mice and the controls (17).

Reducing inflammatory mediators from peritoneal macrophages. COX-2 enzymes are upregulated in response to pro-inflammatory cytokines, particularly in macrophages. This leads to elevated cytokine-mediated PGs, including PGE2 and PGF2α, which are significant in the mechanisms of PTB (60,61). TNF-α and IL-1β are central to the COX-2 pathway, and macrophages, responsible for their production, are suspected to play a role in the local inflammatory mechanism of PTB (8). In the study by Furuya *et al* (17), LPS-exposed peritoneal macrophages exhibited a significant increase in COX-2 mRNA levels for TNF-α and IL-1β. Resveratrol treatment effectively suppressed COX-2 production in these macrophages. This aligns with prior observations in peritoneal washes and cervical tissues by Furuya *et al* (17). Resveratrol reduced TNF-α, IL-1β, and COX-2 mRNA levels in macrophages induced by LPS in a concentration-dependent manner (17). Macrophages play a crucial role in COX-2 production and subsequent PGE2 and PGF2α production. A previous study demonstrated that omega-3 fatty acids, which also have antioxidant and anti-inflammatory properties, can suppress macrophage function and the elevation of PGE2 and PGF2α in gestational tissues induced by LPS (62). These findings collectively suggest that resveratrol primarily targets uterine-associated macrophages, offering the potential to modulate the local inflammatory response in PTB.

Reduction of COX-2 and PGs in the uterus. COX-2 produces PGE2 and PGF2α, potent inducers of uterine contractions and cervical ripening (19). PGs play a pivotal role in cervical maturation and uterine contractions, increasing amniotic fluid during labor (63,64), an essential process in childbirth (65). The upregulation of COX-2 is associated with PTB pathology in both mouse models and humans. The study by Bariani *et al* (8) revealed that LPS-induced uterine inflammation increases COX-2 expression, initiating preterm labor. This upregulation occurs in tissues such as the amnion, choriodecidua, and myometrium, linking it to PTB pathology (66).

The ability of resveratrol to modulate COX-2 expression, a key player in PG production, led to the assessment of uterine PG levels, PGE2, PGF2α, 6-keto-PGF1α and PGI2 (8). Resveratrol has been shown to effectively suppress the LPS-induced elevation of COX-2 in gestational tissues (8). Its administration results in the downregulation of both COX-2 mRNA and protein expression in the uterus, preventing COX-2 gene and protein overexpression induced by LPS (8,67). Notably, LPS alone or in combination with resveratrol does not alter the levels of 15-hydroxyprostaglandin dehydrogenase (15-Pgdh) mRNA and COX-1 protein levels (8), which decrease PG production, counteracting the effects of COX-2 (68). In the study by Bariani *et al* (8), resveratrol administration prevented the increase in uterine PGE2 levels and partially affected PGF2α levels, with no significant impact on the 6-keto-PGF1α concentration (8). The reduction in pro-inflammatory cytokines by resveratrol may explain the lower PG expression, as TNF-α and IL-1β induce PGE2 and PGF2α in choriodecidual tissues (69). In summary, by decreasing PG synthesis, resveratrol exhibits potential in helping to prevent preterm labor.

Reduction of endocannabinoid levels. The endocannabinoid system (ECS) consists of cannabinoid receptors CB1 and CB2, endogenous lipid ligands called endocannabinoids, and regulating enzymes that synthesize and break down these lipids. All endocannabinoids belong to the eicosanoid class (70). Endocannabinoids are unsaturated fatty acid derivatives that interact with this system, eliciting specific responses (71). Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are key endocannabinoids that are released enzymatically from

cell membrane phospholipid precursors in response to various stimuli, including neurotransmitters, depolarizing agents, and hormones (71). AEA is present in the uterus, and its levels in the blood increase during normal labor, suggesting the involvement of the ECS in reproductive and preterm labor processes (72-74). The study by Bariani *et al* (8) demonstrated that LPS and/or resveratrol affected uterine endocannabinoid levels. LPS did not affect the 2-AG levels, but resveratrol alone reduced its levels. AEA increased with LPS, but resveratrol prevented this increase.

The effects of AEA on the uterus are conflicting, with some studies demonstrating the relaxation of the pregnant myometrium (75), while others have reported that the activation of CB1 receptors leads to the increased production of PGE2 in the amnion and choriodecidua (76). CB1 receptor activation is associated with the increased production of PGF2α in inflammation-induced preterm labor (77). Prolonged endocannabinoid signaling is linked to adverse pregnancy outcomes (78). Bariani *et al* (8) found that LPS altered AEA and related endocannabinoid-like lipid levels in the uterus, consistent with previous research (75,76). LPS-induced cytokines can affect endocannabinoid production by modulating the expression and activity of fatty acid amide hydrolase (FAAH) (79,80). In the study by Bariani *et al* (8) treatment with resveratrol restored AEA and other lipid levels to the control levels, although the exact mechanisms involved remain unclear. The increased AEA production induced by LPS was associated with a higher incidence of preterm labor, while the tocolytic effects of resveratrol correlated with reduced uterine AEA content (8).

Bariani *et al* (8) discovered that LPS increased the AEA levels in the uterus, resulting in a greater likelihood of preterm labor. However, resveratrol prevented this increase, indicating its tocolytic effect in reducing uterine endocannabinoids during inflammation (8). In addition to endocannabinoids, endocannabinoid-like lipids from the N-acyl ethanolamine, N-arachidonoyl glycine (NAGlys), N-arachidonoyl serine (NASers) and 2-acyl-sn-glycerols families can undergo changes in composition during LPS-induced pregnancy inflammation (8). The specific molecular mechanism through which resveratrol modifies uterine endocannabinoids and lipid composition remains unclear. However, it is known that NAGlys and NASers, which are part of these lipids, do not activate CB1 or CB2 receptors (81). NASers have been observed to regulate calcium-activated potassium channels (82) and N-type calcium channels (83). Additionally, NAGlys can be metabolized by COX-2 and FAAH, potentially functioning as endogenous enzyme inhibitors (84).

There was a 1.5-fold increase in the average plasma levels of AEA from 1.20±0.57 nM in non-labor conditions to 1.82±0.87 nM during labor ($P<0.0001$) (72). A plasma AEA concentration exceeding 1.095 nM was found to be a better predictor of PTB before 37 weeks of gestation compared to currently used predictors, such as cervical length, oncofetal fibronectin and cervical insulin-like growth factor binding protein 1. It demonstrated 87.14% specificity, 25.93% sensitivity, a 70.24% negative predictive value (NPV), and a 61.2% positive predictive value (PPV), surpassing existing predictive tests (85). The average plasma AEA level significantly increased in women with a positive fetal fibronectin test compared to those with a negative result, providing additional evidence of the role of AEA in labor and its potential use as a predictor for PTB (85). AEA levels are regulated through cellular uptake by the AEA transporter and enzymatic degradation by FAAH on the cell membrane (86). LPS-induced cytokines influence endocannabinoid production by affecting FAAH protein expression and enzymatic activity (87). Anti-inflammatory cytokines (IL-4 and IL-10) enhance FAAH activity, while pro-inflammatory cytokines (IL-12 and IFN-γ) reduce FAAH activity and protein expression in peripheral mononuclear cells (lymphocytes) (8,88). During pregnancy, FAAH levels in peripheral mononuclear cells show an inverse correlation with blood AEA levels (89). Low AEA levels with high FAAH are crucial for the successful development of pregnancy (90,91). The reduced activity and expression of anandamide hydrolase in peripheral lymphocytes can serve as an early indication of spontaneous abortion before eight weeks of gestation, offering potential diagnostic utility for pregnancy monitoring and fertility assessment (91).

Modulating 5' AMP-activated protein kinase (AMPK) and mammalian target of rapamycin complex (mTORC) pathways. Inflammation and oxidative stress are widely recognized risk factors for PTB. Studies conducted on mouse models, specifically those with spontaneous and inflammation-induced PTB with *p53* deletion ($p53^{d/d}$ females), have indicated the involvement of mTOR activation in decidual senescence and the excessive production of PGs derived from COX2, ultimately leading to PTB (11). In female mice with the $p53^{d/d}$ phenotype, a noticeable decrease in the growth of uterine decidual cells due to accelerated senescence has been observed (92,93). This condition is accompanied by elevated levels of pAkt, p21, IL-8 and various CXCL cytokines, collectively contributing to the senescence-associated secretory phenotype, which further promotes decidual senescence and PTB (93). Additionally, this *p53* deletion has been associated with PTB, which can also be influenced by factors, such as increased ROS production due to conditions such as pre-eclampsia, as well as environmental factors such as smoking and pollution (93).

Deng *et al* (11) demonstrated that resveratrol, an antioxidant and anti-aging agent, activated AMPK signaling and inhibited mTORC1 signaling in decidual cells without causing any adverse effects on the mother or offspring. Consequently, resveratrol offers protection against both spontaneous and inflammation-induced PTB in $p53^{d/d}$ females. Similar beneficial effects have also been observed with the use of AMPK activators such as metformin, which enhances decidual health and reduces PTB rates in mouse models (11). Human fetal membranes contain both AMPK and its phosphorylated form (p-AMPK). Membranes obtained from spontaneous term labor and pre-labor rupture display significantly lower levels of p-AMPK compared to intact membranes (11). Pre-treatment of human fetal membranes with AMPK activators reduces the production of inflammatory cytokines in response to LPS, indicating the anti-inflammatory effects of p-AMPK on fetal membranes (94). Resveratrol decreases PGE2 levels by suppressing Ptgs2, the COX2-encoding gene, in decidual cells. It also inhibits hyperactive mTORC1 through both AMPK-dependent and/or AMPK-independent pathways, underscoring its role in the regulation of AMPK and mTORC1 signaling in an inverse manner (95).

Other potential benefits of resveratrol: Smooth muscle relaxation. Resveratrol has the ability to relax smooth muscle, which may have an impact on PTB by targeting potassium (K^+) channels (31,96-98). The proper functioning of K^+ channels is crucial for maintaining a relaxed uterine state during pregnancy by aiding in membrane repolarization (99). The dysregulation of K^+ channels can lead to abnormal uterine activity, contributing to conditions such as preterm labor (31). Poorly functioning or less active K^+ channels can decrease the repolarizing current in myometrial smooth muscle cells, resulting in untimely uterine contractions and preterm delivery. Conversely, excessive expression of K^+ channels in the later stages of pregnancy may hinder synchronized uterine muscle activity needed for full-term labor (98). Various types of K^+ channels, including big Ca^{2+}-sensitive K^+ (BKCa) channels, ATP-sensitive K^+ (KATP) channels, Kv channels and SK channels, induce relaxation in both non-pregnant and pregnant myometrium, demonstrating the complex regulation of uterine tone (31,96-98). BKCa channels, which hold a particular influence on uterine smooth muscle, play a significant role in inducing smooth muscle relaxation and repolarizing K^+ current (99). Their activity varies throughout pregnancy, and their modulation is regulated by 17b-estradiol (31). BKCa channels have a more pronounced relaxant effect during mid-gestation (100,101), indicating their importance in maintaining uterine quiescence (99).

The regulation of myometrial tone during pregnancy involves the modulation of ion channels. β-receptor agonists, used to delay preterm labor, interact with BKCa channels via ß2- and ß3-receptors, resulting in uterine relaxation (99). Human studies suggest increased levels of BKCa channel in late pregnant non-laboring myometrium but decreased expression in preterm and term laboring myometrium (99). KATP channels, composed of Kir6 channels and sulfonylurea receptors, play a role in myometrial quiescence; however, their specific function in the myometrium is not yet clear. The downregulation of KATP channels, particularly Kir6.1 and SUR2B subunits, may increase uterine excitability and labor contractions in term pregnancy (101). The regulation of KATP channels varies with the stage of gestation and the incidence of labor contractions in the human myometrium, necessitating further research for a comprehensive understanding (101). Aberrant K channel function or expression is associated with conditions such as PTB and preeclampsia (96,102). Resveratrol can modulate K channel activity, potentially offering new treatments for these conditions by reducing intracellular calcium levels and inhibiting various contractions (31). Resveratrol effectively inhibits uterine smooth muscle contractions, which can lead to infertility, endometriosis, miscarriage, or PTB (31,96,97,99). It targets KATP, BKCa and Kv channels to achieve relaxation effects on the uterus (97). This relaxation potential extends to pregnancy-related disorders, such as PTB, by relaxing the myometrial smooth muscle and fetoplacental blood vessels, inhibiting contractions induced by oxytocin, PGs and acetylcholine (96).

Efficacy of resveratrol in preventing preterm birth. Resveratrol shows promise as an herbal preventive agent for PTB. In the study by Bariani *et al* (8), the administration of resveratrol resulted in a 64% reduction in PTB rates and a 28% decrease in mortality rates. These effects may be attributed to resveratrol's impact on uterine NOS activity, iNOS expression, COX-2, PGE2, and AEA profiling. Additionally, this treatment led to a decrease in antepartum hemorrhage, fetal toxicity, and offspring mortality. Importantly, mice treated with resveratrol did not experience vaginal bleeding, and their uterine morphology improved (8). Deng *et al* (11) demonstrated that resveratrol has the potential to prevent PTB through its modulation of AMPK and mTORC1 signaling in decidual cells. The administration of resveratrol offers several advantages, including no adverse effects on pregnancy outcomes, effective targeting of decidual health, and compensation for ovarian luteolysis (11). The study conducted by Furuya *et al* (17) also supports the tocolytic effects of resveratrol by suppressing peritoneal macrophage-induced inflammation and preventing spontaneous PTB in a genetic model of accelerated decidual senescence.

Furthermore, Furuya *et al* (17) discovered that resveratrol had a significant impact on reducing the rate of PTB in mice. At a dosage of 20 mg/kg, the PTB rate was 48.6±19.4% compared to 97.8±1.9% in the control group (P=0.03). Morever, at a dosage of 40 mg/kg, the PTB rate was 57.1±13.8% compared to 83.7±13.2% in the control group (P=0.15). By orally administering resveratrol, the occurrence of LPS-induced prematurity in mice was reduced through the suppression of inflammatory mediators, PGs, peritoneal macrophages and endocannabinoid compounds in the maternal reproductive organs (17). Novaković *et al* (31) demonstrated that resveratrol effectively prevents PTB by inhibiting uterine contractions, including those stimulated by oxytocin. Resveratrol achieves this by regulating various myometrial K^+ channels, such as KATP, Kv and BKCa channels, by increasing intracellular Ca^{2+} levels. Moreover, it induces partial relaxation of the myometrium by activating Kir6.2/SUR1 channels. Nonetheless, there are certain limitations to consider, such as the failure of a single resveratrol treatment to prevent PTB in the study conducted by Deng *et al* (11) and its lack of effectiveness against tonic contractions induced by oxytocin (31).

Pharmacological profile of resveratrol: From bench to bedside. Oral resveratrol is readily absorbed but undergoes rapid metabolism (102). Azachi *et al* (103) conducted a study in which red grape cell (RGC) resveratrol exhibited two plasma concentration peaks: One at 1 h following administration and another at 5 h following administration. The initial peak is likely a result of the extensive glucuronidation and sulfation of resveratrol in the enterocytes of the small intestine. By contrast, the second peak occurs due to the flow of bile-containing metabolites from the liver to the intestines, a normal occurrence after food consumption that may prolong the pharmacological effect of certain substances and their metabolites (103,104).

The median time to peak drug concentration (T_{max}) for total resveratrol at a dose of 150 mg RGC is 4 h (range, 0.67-6.00), and at 50 mg it is 1 h (range, 0.33-8.00). Moreover, the median T_{max} for free resveratrol at a dose of 150 mg RGC is 1 h (range, 0.33-4.00) (103). Resveratrol exhibits a high oral absorption but rapid metabolism, resulting in poor overall bioavailability. Even with a high dose of 5 g, it only reaches a peak plasma-free concentration of 538 ng/ml. This limited bioavailability

may be attributed to low solubility, similar to other polyphenol aglycones, which struggle to form hydrogen bonds due to hydrophobic interactions with hydroxyl or aromatic groups (103). One approach to enhance solubility is through glycosylation of the resveratrol parent compound (103).

Resveratrol interacts with cytochrome P450 enzymes, inhibiting CYP3A4, CYP2D6 and CYP2C9, while inducing CYP1A2, potentially affecting drugs metabolized by these enzymes (105). Urinary excretion studies demonstrate high absorption rates (at least 70%) after oral resveratrol intake, with 53.4 to 84.9% of total radioactivity recovered in urine. However, rapid biotransformation leads to minimal unmodified resveratrol in circulation and relatively high levels (maximum, 2 μM) of resveratrol metabolites after a 25 mg oral dose, resulting in near-zero resveratrol bio-availability (104). The intravenous injection of a 0.2 mg dose shows no second peak and a rapid decline in plasma total radioactivity over the first hour, indicating extensive distribution. Plasma half-life durations are similar after both routes (9.2 h orally and 11.4 h intravenously), with dose-dependent resveratrol plasma levels reaching up to 530 ng/ml with higher doses (up to 5 g) (104). The administration of resveratrol during pregnancy appears to be relatively safe for both the mother and fetus, with no reported toxicity or adverse pregnancy outcomes (11,102).

Resveratrol is primarily sourced from grapes, grape skins, peanuts, red wine, cranberries and Japanese knotweed (*Polygonum cuspidatum*) (102,105). The quantity of resveratrol varies among these sources. For example, RGCs contain between 726 to 916 mg/kg (103), while agricultural red grapes range from 0 to 42.5 mg/kg (103). Other examples include jamun fruit with 11.19 to 34.87 mg/g of dry weight, mulberries with 35.8 to 50.61 mg/g, jackfruit with 0.07 to 3.56 mg/g (106), apples with 47 mg/g, broccoli with 18 mg/g, onions with 18 mg/g and black tea with 11.3 mg/g (107). Typical concentrations of resveratrol in various food products to meet the recommended daily allowance (RDA) of 1 g are as follows: Red grapes (92-1,604 mg/kg fresh weight), white grapes (59-1,759 mg/kg fresh weight), peanuts without seed coats (0.03-0.14 mg/g), red wines (0.361-1.972 mg/l), white wines (0-1.089 mg/l), rosé wines (0.29 mg/l), beers (1.34-77.0 mg/l), tomato skins (19 mg/g dry weight), dark chocolate (350 mg/kg), milk chocolate (100 mg/kg), Itadori tea (68 mg/100 ml) and apples (400 mg/kg fresh weight) (108).

Due to its limited solubility in water, resveratrol is primarily absorbed through passive diffusion in the colon and undergoes significant pre-systemic metabolism in the liver. This liver metabolism markedly reduces the levels of free resveratrol before it enters systemic circulation. Resveratrol is conjugated to more soluble glucuronides (e.g., resveratrol-3-O-glucuronide, resveratrol-4-O-glucuronide) and sulfates (e.g., resveratrol-trisulfate) in phase II metabolism or binds to albumin and lipoproteins. As a result, the therapeutic effectiveness of oral resveratrol is relatively low. Efforts to improve the bioavailability of resveratrol or delay its phase II metabolism through the use of resveratrol prodrugs are crucial for its biomedical applications (108,109).

The oral supplementation of 80 mg resveratrol in overweight pregnant women has demonstrated a reduction in the incidence of gestational diabetes mellitus, improvement in lipid profiles, and a decrease in glucose levels within a 60-day period. Additionally, resveratrol administration at a dose of 50 mg for up to 5 doses has been found to lower blood pressure in patients with preeclampsia (102). However, it should be noted that there is limited clinical research available on the use of resveratrol during pregnancy, with more extensive studies available for patients with diabetes, cardiovascular issues and metabolic disorders (105). Challenges in the clinical application of resveratrol include the wide range of dosages used (ranging from 5 mg to 5 g daily), the diverse dose-effect associations observed in the SIRT1 pathway, concerns regarding renal toxicity associated with micronized oral formulations such as SRT501 (commercially marketed as a supplement, rather than a definitive treatment drug) and gastrointestinal side-effects at high doses. Furthermore, it has been observed that resveratrol can activate estrogen-regulated genes that are associated with estrogen-dependent neoplasms (105).

Strength and limitations. This presented systematic review highlights a unique academic perspective on the prevention of PTB using resveratrol. It offers original contributions to the field of preclinical investigations of natural compound medicine for PTB. Notably, to the best of our knowledge, this systematic review is the first to specifically examine the impact of resveratrol in preventing PTB and highlights its promising benefits. The present study goes beyond a mere summary of the literature by providing a comprehensive framework that explains the preventive mechanisms of resveratrol. It also includes a visualized image that consolidates the scattered literature. By adopting this approach, the present study contributes significantly to the development of strategies to combat PTB. Furthermore, the present study stands out for its meticulous quality assessment, employing stringent predetermined criteria to critically evaluate the included studies.

In the present systematic review, the authors were not able to conduct a meta-analysis due to two main reasons. First, there was a limited number of articles included, which makes it impractical. Second, the data and results presented in these studies were presented in a heterogeneous manner, rendering it impossible to pool the data. The main limitation of this systematic review was the diverse nature of how data and results are presented across the included studies, which prevents a meta-analysis from being practically feasible. Additionally, while the significant prevalence of favorable outcomes in the present systematic review is encouraging, it is important to consider the possibility of publication bias, where studies with unfavorable results may remain unpublished. Furthermore, the strict inclusion criteria resulted in the exclusion of several studies that did not directly involve resveratrol in PTB. Nonetheless, the insights from these excluded studies are still integrated into the discussion section, adding to the broader conversation on the subject.

Despite the potential of resveratrol as a tocolytic agent for preventing PTB, particularly in cases involving intrauterine inflammation, there is a scarcity of human studies evaluating its effectiveness in this regard, and no current human clinical trials have been conducted, at least to the best of our knowledge. While mouse models provide valuable information, their limitations stem from significant anatomical and physiological differences compared to humans, and findings from *in vitro* and *in vivo* studies may not directly translate to

human outcomes due to inherent species disparities. However, this juncture presents an opportune moment for researchers to validate the potential benefits of resveratrol through dedicated human studies. The current insights from various models offer valuable information about labor and delivery mechanisms, underscoring the need for well-designed prospective studies to assess the efficacy of resveratrol in human populations.

In conclusion, the findings presented herein indicate that resveratrol may have the ability to prevent preterm labor induced by LPS by inhibiting pro-inflammatory mediators, reducing PG levels, improving endocannabinoid profiles, relaxing smooth muscle and preventing excessive uterine contractions through ion channels. Considering its ability to cross the placenta, future studies are required to investigate its potential protective effects on embryos. Moreover, a better understanding of the role of resveratrol in human or similar uterine physiology necessitates further investigation. Urgent clinical trials are necessary to determine the optimal dosage of resveratrol for PTB therapy using standardized formulations. Given the low oral bioavailability of resveratrol, improving its pharmacological properties is pivotal. Structural optimization and the use of resveratrol-encapsulated nanoparticles can enhance efficacy, reduce dosages, minimize side-effects and target specific organs. Additionally, exploring the potential of locally derived resveratrol from plants and conducting oligomer research shows promise. Long-term studies are required to substantiate the scientific potential of resveratrol.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MH served as the principal investigator for the present study, conceiving the research and making the decision to publish. In the role of guarantor, MH took full responsibility for the work. MH, MIDR, and ABP jointly designed the methodology. MH, MIDR and ABP conducted the investigation, had complete access to the literature data, contributed to data analysis and curation, drafted the manuscript and secured funding. MH and ABP utilized software to create visualizations of the study findings and managed the project. Additionally, MH provided resources, validated all evidence analyses and supervised the study process meticulously. MH, MIDR and ABP confirm the authenticity of all the raw data. All authors have read and approved the final version for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. World Health Organization (WHO): Factsheet of Preterm Birth. WHO, Geneva, 2018. https://www.who.int/news-room/fact-sheets/detail/preterm-birth.
2. Pan American Health Organization (PAHO): 152 million babies born preterm in the last decade. PAHO, Washington, DC, 2013. https://www.paho.org/en/news/15-6-2023-152-million-babies-born-preterm-last-decade#:~:text=An%20estimated%2013.4%20million%20babies,37%20weeks%20of%20pregnancy)%20worldwide. Accessed Sep 28, 2023.
3. Cao G, Liu J and Liu M: Global, regional, and national incidence and mortality of neonatal preterm birth, 1990-2019. JAMA Pediatr 176: 787, 2022.
4. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J and Oei JL; New South Wales and Australian Capital Territory Neonatal Intensive Care Units' Data Collection: Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 133: 55-62, 2014.
5. Beam AL, Fried I, Palmer N, Agniel D, Brat G, Fox K, Kohane I, Sinaiko A, Zupancic JAF and Armstrong J: Estimates of healthcare spending for preterm and low-birthweight infants in a commercially insured population: 2008-2016. J Perinatol 40: 1091-1099, 2020.
6. Romero R, Dey SK and Fisher SJ: Preterm labor: One syndrome, many causes. Science 345: 760-765, 2014.
7. Bastek JA, Gómez LM and Elovitz MA: The role of inflammation and infection in preterm birth. Clin Perinatol 38: 385-406, 2011.
8. Bariani MV, Correa F, Leishman E, Domínguez Rubio AP, Arias A, Stern A, Bradshaw HB and Franchi AM: Resveratrol protects from lipopolysaccharide-induced inflammation in the uterus and prevents experimental preterm birth. Mol Hum Reprod 23: 571-581, 2017.
9. Tency I: Inflammatory response in maternal serum during preterm labour. Facts Views Vis Obgyn 6: 19-30, 2014.
10. Elovitz MA, Wang Z, Chien EK, Rychlik DF and Phillippe M: A new model for Inflammation-Induced preterm birth. Am J Pathol 163: 2103-2111, 2003.
11. Deng W, Cha J, Yuan J, Haraguchi H, Bartos A, Leishman E, Viollet B, Bradshaw HB, Hirota Y and Dey SK: p53 coordinates decidual sestrin 2/AMPK/mTORC1 signaling to govern parturition timing. J Clin Invest 126: 2941-2954, 2016.
12. Simhan HN and Caritis SN: Prevention of preterm delivery. N Engl J Med 357: 477-487, 2007.
13. Abramovici A, Cantu J and Jenkins SM: Tocolytic therapy for acute preterm labor. Obstet Gynecol Clin North Am 39: 77-87, 2012.
14. Alfirevic Z: Tocolytics: Do they actually work? BMJ 345: e6531-e6531, 2012.
15. Croen LA, Connors SL, Matevia M, Qian Y, Newschaffer C and Zimmerman AW: Prenatal exposure to β2-adrenergic receptor agonists and risk of autism spectrum disorders. J Neurodev Disord 3: 307-315, 2011.
16. Gidaya NB, Lee BK, Burstyn I, Michael Y, Newschaffer CJ and Mortensen EL: In utero exposure to β-2-Adrenergic receptor agonist drugs and risk for autism spectrum disorders. Pediatrics 137: e20151316, 2016.
17. Furuya H, Taguchi A, Kawana K, Yamashita A, Inoue E, Yoshida M, Nakamura H, Fujimoto A, Inoue T, Sato M, *et al*: Resveratrol protects against pathological preterm birth by suppression of Macrophage-Mediated Inflammation. Reprod Cie 22: 1561-1568, 2015.
18. Bourque SL, Dolinsky VW, Dyck JRB and Davidge ST: Maternal resveratrol treatment during pregnancy improves adverse fetal outcomes in a rat model of severe hypoxia. Placenta 33: 449-452, 2012.
19. Poudel R, Stanley JL, Rueda-Clausen CF, Andersson IJ, Sibley CP, Davidge ST and Baker PN: Effects of resveratrol in pregnancy using murine models with reduced blood supply to the uterus. PLoS One 8: e64401, 2013.

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
21. Schneider K, Schwarz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, Hartung T and Hoffmann S: 'ToxRTool', a new tool to assess the reliability of toxicological data. Toxicol Lett 189: 138-144, 2009.
22. Valenti C, Billi M, Pancrazi GL, Calabria E, Armogida NG, Tortora G, Pagano S, Barnaba P and Marinucci L: Biological effects of cannabidiol on human cancer cells: Systematic review of the literature. Pharmacol Res 181: 106267, 2022.
23. Moser VC, Morris-Schaffer K, Richardson JR and Li AA: Glyphosate and neurological outcomes: A systematic literature review of animal studies. J Toxicol Environ Health B Crit Rev 25: 162-209, 2022.
24. Gupta M, Singh D, Rastogi S, Siddique HR, Al-Dayan N, Ahmad A, Sikander M and Sarwat M: Anti-cancer activity of guggulsterone by modulating apoptotic markers: A systematic review and meta-analysis. Front Pharmacol 14: 1155163, 2023.
25. EU Science Hub: ToxRTool-Toxicological data reliability assessment tool. In: European Commission for Scientific Tools and Databases. European Commission, 2023. https://joint-research-centre.ec.europa.eu/scientific-tools-and-databases/toxrtool-toxicological-data-reliability-assessment-tool_en. Accessed Sep 21, 2023.
26. University of Pittsburgh: Health Research Reporting Guidelines, Study Execution Manuals, Critical Appraisal, Risk of Bias, and Non-reporting Biases: From Cochrane Handbook for Systematic Reviews of Interventions [Internet]. University of Pittsburgh: Health Sciences Library System Guides, 2023. https://hsls.libguides.com/reporting-study-tools/risk-of-bias. Accessed Sep 21, 2023.
27. Osmanovic A, Halilovic S, Kurtovic-Kozaric A and Hadziabdic N: Evaluation of periodontal ligament cell viability in different storage media based on human PDL cell culture experiments-A systematic review. Dental Traumatol 34: 384-393, 2018.
28. National Toxicology Program: Handbook for conducting a literature-based health assessment using OHAT approach for systemic review and evidence integration. National Institute of Environmental Health Science, pp1-102, 2019.
29. Puidokas T, Kubilius M, Stumbras A and Juodzbalys G: Effect of leukocytes included in platelet concentrates on cell behaviour. Platelets 30: 937-945, 2019.
30. Center for Evidence-Based Medicine (CEBM): OCEMB Levels of Evidence. CEBM, Oxford, 2011. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence. Accessed Sep 21, 2023.
31. Novaković R, Radunović N, Marković-Lipkovski J, Ćirović S, Beleslin-Čokić B, Ilić B, Ivković B, Heinle H, Živanović V and Gojković-Bukarica LJ: Effects of the polyphenol resveratrol on contractility of human term pregnant myometrium. Mol Hum Reprod 21: 545-551, 2015.
32. Wilson A, Hodgetts-Morton VA, Marson EJ, Markland AD, Larkai E, Papadopoulou A, Coomarasamy A, Tobias A, Chou D, Oladapo OT, *et al*: Tocolytics for delaying preterm birth: A network meta-analysis. Cochrane Database Syst Rev 8: CD014978, 2022.
33. Abd El-Mohsen M, Bayele H, Kuhnle G, Gibson G, Debnam E, Kaila Srai S, Rice-Evans C and Spencer JP: Distribution of [3H] trans-resveratrol in rat tissues following oral administration. Br J Nutr 96: 62-70, 2006.
34. Walle T, Hsieh F, DeLegge MH, Oatis JE and Walle UK: High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos 32: 1377-1382, 2004.
35. Walle T: Bioavailability of resveratrol. Ann N Y Acad Sci 1215: 9-15, 2011.
36. la Porte C, Voduc N, Zhang G, Seguin I, Tardiff D, Singhal N and Cameron DW: Steady-State pharmacokinetics and tolerability of Trans-Resveratrol 2000 mg twice daily with food, quercetin and alcohol (Ethanol) in healthy human subjects. Clin Pharmacokinet 49: 449-454, 2010.
37. Brown VA, Patel KR, Viskaduraki M, Crowell JA, Perloff M, Booth TD, Vasilinin G, Sen A, Schinas AM, Piccirilli G, *et al*: Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: Safety, pharmacokinetics, and effect on the Insulin-like growth factor axis. Cancer Res 70: 9003-9011, 2010.
38. Gracie S, Pennell C, Ekman-Ordeberg G, Lye S, McManaman J, Williams S, Palmer L, Kelley M, Menon R and Gravett M; PREBIC '-Omics' Research Group: An integrated systems biology approach to the study of preterm birth using '-omic' technology-a guideline for research. BMC Pregnancy Childbirth 11: 71, 2011.
39. Green ES and Arck PC: Pathogenesis of preterm birth: Bidirectional inflammation in mother and fetus. Semin Immunopathol 42: 413-429, 2020.
40. McCarthy R, Martin-Fairey C, Sojka DK, Herzog ED, Jungheim ES, Stout MJ, Fay JC, Mahendroo M, Reese J, Herington JL, *et al*: Mouse models of preterm birth: Suggested assessment and reporting guidelines. Biol Reprod 99: 922-937, 2018.
41. Romero R and Tartakovsky B: The natural interleukin-1 receptor antagonist prevents interleukin-1-induced preterm delivery in mice. Am J Obstet Gynecol 167: 1041-1045, 1992.
42. Robertson SA, Christiaens I, Dorian CL, Zaragoza DB, Care AS, Banks AM and Olson DM: Interleukin-6 is an essential determinant of on-time parturition in the mouse. Endocrinology 151: 3996-4006, 2010.
43. Montalbano AP, Hawgood S and Mendelson CR: Mice deficient in surfactant protein A (SP-A) and SP-D or in TLR2 manifest delayed parturition and decreased expression of inflammatory and contractile genes. Endocrinology 154: 483-498, 2013.
44. Gonzalez JM, Franzke CW, Yang F, Romero R and Girardi G: Complement activation triggers metalloproteinases release inducing cervical remodeling and preterm birth in mice. Am J Pathol 179: 838-849, 2011.
45. Wahid HH, Dorian CL, Chin PY, Hutchinson MR, Rice KC, Olson DM, Moldenhauer LM and Robertson SA: Toll-Like Receptor 4 Is an essential upstream regulator of On-Time parturition and perinatal viability in mice. Endocrinology 156: 3828-3841, 2015.
46. Krediet TG, Wiertsema SP, Vossers MJ, Hoeks SBEA, Fleer A, Ruven HJ and Rijkers GT: Toll-like receptor 2 polymorphism is associated with preterm birth. Pediatr Res 62: 474-476, 2007.
47. Bayar E, Bennett PR, Chan D, Sykes L and MacIntyre DA: The pregnancy microbiome and preterm birth. Semin Immunopathol 42: 487-499, 2020.
48. Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R and Conner M: Interconceptional antibiotics to prevent spontaneous preterm birth: A randomized clinical trial. Am J Obstet Gynecol 194: 617-623, 2006.
49. Abedini E, Khodadadi E, Zeinalzadeh E, Moaddab SR, Asgharzadeh M, Mehramouz B, Dao S and Samadi Kafil H: A comprehensive study on the antimicrobial properties of resveratrol as an alternative therapy. Evid Based Complement Alternat Med 2021: 8866311, 2021.
50. Ma DSL, Tan LTH, Chan KG, Yap WH, Pusparajah P, Chuah LH, Ming LC, Khan TM, Lee LH and Goh BH: Resveratrol-Potential antibacterial agent against foodborne pathogens. Front Pharmacol 9: 102, 2018.
51. Roberts RA, Laskin DL, Smith CV, Robertson FM, Allen EMG, Doorn JA and Slikker W: Nitrative and oxidative stress in toxicology and disease. Toxicol Sci 112: 4-16, 2009.
52. Meng T, Xiao D, Muhammed A, Deng J, Chen L and He J: Anti-Inflammatory action and mechanisms of resveratrol. Molecules 26: 229, 2021.
53. Gómez-Chávez F, Correa D, Navarrete-Meneses P, Cancino-Diaz JC, Cancino-Diaz ME and Rodríguez-Martínez S: NF-κB and its regulators during pregnancy. Front Immunol 12: 679106, 2021.
54. Malaguarnera: Influence of resveratrol on the immune response. Nutrients 11: 946, 2019.
55. Liu T, Zhang L, Joo D and Sun SC: NF-κB signaling in inflammation. Signal Transduct Target Ther 2: 17023, 2017.
56. Klawitter M, Hakozaki M, Kobayashi H, Krupkova O, Quero L, Ospelt C, Gay S, Hausmann O, Liebscher T, Meier U, *et al*: Expression and regulation of toll-like receptors (TLRs) in human intervertebral disc cells. Eur Spine J 23: 1878-1891, 2014.
57. Lappas M, Mitton A, Lim R, Barker G, Riley C and Permezel M: SIRT1 Is a novel regulator of key pathways of human labor1. Biol Reprod 84: 167-178, 2011.
58. Manna SK, Mukhopadhyay A and Aggarwal BB: Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: Potential role of reactive oxygen intermediates and lipid peroxidation. J Immunol 164: 6509-6519, 2000.
59. Zhu X, Liu Q, Wang M, Liang M, Yang X, Xu X, Zou H and Qiu J: Activation of sirt1 by resveratrol inhibits TNF-α induced inflammation in fibroblasts. PLoS One 6: e27081, 2011.

60. Taguchi A, Yamashita A, Kawana K, Nagamatsu T, Furuya H, Inoue E, Osuga Y and Fujii T: Recent progress in therapeutics for inflammation-associated preterm birth: A review. Reprod Sci 24: 7-18, 2017.
61. Taguchi A, Wada-Hiraike O, Kawana K, Koga K, Yamashita A, Shirane A, Urata Y, Kozuma S, Osuga Y and Fujii T: Resveratrol suppresses inflammatory responses in endometrial stromal cells derived from endometriosis: A possible role of the sirtuin 1 pathway. J Obstet Gynaecol Res 40: 770-778, 2014.
62. Vidal MS, Lintao RCV, Severino MEL, Tantengco OAG and Menon R: Spontaneous preterm birth: Involvement of multiple feto-maternal tissues and organ systems, differing mechanisms, and pathways. Front Endocrinol (Lausanne) 13: 1015622, 2022.
63. Wood EM, Hornaday KK and Slater DM: Prostaglandins in biofluids in pregnancy and labour: A systematic review. PLoS One 16: e0260115, 2021.
64. Yamashita A, Kawana K, Tomio K, Taguchi A, Isobe Y, Iwamoto R, Masuda K, Furuya H, Nagamatsu T, Nagasaka K, *et al*: Increased tissue levels of omega-3 polyunsaturated fatty acids prevents pathological preterm birth. Sci Rep 3: 3113, 2013.
65. Li WJ, Lu JW, Zhang CY, Wang WS, Ying H, Myatt L and Sun K: PGE2 vs PGF2α in human parturition. Placenta 104: 208-219, 2021.
66. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, Navaratnam K and Caldwell DM: Labour induction with prostaglandins: A systematic re view and network meta-analysis. BMJ 350: h217, 2015.
67. Sykes L, MacIntyre DA, Teoh TG and Bennett PR: Anti-inflammatory prostaglandins for the prevention of preterm labour. Reproduction 148: R29-R40, 2014.
68. Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss JF and Petraglia F: Inflammation and Pregnancy. Reprod Sci 16: 206-215, 2009.
69. Zhang Y, Desai A, Yang SY, Bae KB, Antczak MI, Fink SP, Tiwari S, Willis JE, Williams NS, Dawson DM, *et al*: Inhibition of the prostaglandin-degrading enzyme 15-PGDH potentiates tissue regeneration. Science 348: aaa2340, 2015.
70. Mitchell MD, Rice GE, Vaswani K, Kvaskoff D and Peiris HN: Differential regulation of eicosanoid and endocannabinoid production by inflammatory mediators in human choriodecidua. PLoS One 11: e0148306, 2016.
71. Maia J, Fonseca B, Teixeira N and Correia-da-Silva G: The fundamental role of the endocannabinoid system in endometrium and placenta: Implications in pathophysiological aspects of uterine and pregnancy disorders. Hum Reprod Update 26: 586-602, 2020.
72. Nallendran V, Lam PM, Marczylo TH, Bankart MJ, Taylor AH, Taylor DJ and Konje JC: The plasma levels of the endocannabinoid, anandamide, increase with the induction of labour. BJOG 117: 863-869, 2010.
73. Bariani MV, Domínguez Rubio AP, Cella M, Burdet J, Franchi AM and Aisemberg J: Role of the endocannabinoid system in the mechanisms involved in the LPS-induced preterm labor. Reproduction 150: 463-472, 2015.
74. Komarnytsky S, Rathinasabapathy T, Wagner C, Metzger B, Carlisle C, Panda C, Le Brun-Blashka S, Troup JP and Varadharaj S: Endocannabinoid system and its regulation by polyunsaturated fatty acids and full spectrum hemp oils. Int J Mol Sci 22: 5479, 2021.
75. Rava A and Trezza V: Emerging roles of endocannabinoids as key lipid mediators for a successful pregnancy. Int J Mol Sci 24: 5220, 2023.
76. Dennedy MC, Friel AM, Houlihan DD, Broderick VM, Smith T and Morrison JJ: Cannabinoids and the human uterus during pregnancy. Am J Obstet Gynecol 190: 2-9, 2004.
77. Mitchell MD, Sato TA, Wang A, Keelan JA, Ponnampalam AP and Glass M: Cannabinoids stimulate prostaglandin production by human gestational tissues through a tissue- and CB1-receptor-specific mechanism. Am J Physiol Endocrinol Metab 294: E352-E356, 2008.
78. Kozakiewicz ML, Grotegut CA and Howlett AC: Endocannabinoid system in pregnancy maintenance and labor: A mini-review. Front Endocrinol (Lausanne) 12: 699951, 2021.
79. Booker L, Kinsey SG, Abdullah RA, Blankman JL, Long JZ, Ezzili C, Boger DL, Cravatt BF and Lichtman AH: The fatty acid amide hydrolase (FAAH) inhibitor PF-3845 acts in the nervous system to reverse LPS-induced tactile allodynia in mice. Br J Pharmacol 165: 2485-2496, 2012.
80. Sun X, Deng W, Li Y, Tang S, Leishman E, Bradshaw HB and Dey SK: Sustained endocannabinoid signaling compromises decidual function and promotes inflammation-induced preterm birth. J Biol Chem 291: 8231-8240, 2016.
81. Donvito G, Nass SR, Wilkerson JL, Curry ZA, Schurman LD, Kinsey SG and Lichtman AH: The endogenous cannabinoid system: A budding source of targets for treating inflammatory and neuropathic pain. Neuropsychopharmacology 43: 52-79, 2018.
82. Connor M, Vaughan CW and Vandenberg RJ: N-Acyl amino acids and N-acyl neurotransmitter conjugates: Neuromodulators and probes for new drug targets. Br J Pharmacol 160: 1857-1871, 2010.
83. Godlewski G, Offertáler L, Osei-Hyiaman D, Mo FM, Harvey-White J, Liu J, Davis MI, Zhang L, Razdan RK, Milman G, *et al*: The endogenous brain constituent N-Arachidonoyl l-Serine Is an activator of large conductance Ca 2+-Activated K+ channels. J Pharmacol Exp Ther 328: 351-361, 2009.
84. Guo J, Williams DJ and Ikeda SR: N-Arachidonoyl L-Serine, a putative endocannabinoid, alters the activation of N-Type Ca2+ Channels in sympathetic neurons. J Neurophysiol 100: 1147-151, 2008.
85. Grazia Cascio M, Minassi A, Ligresti A, Appendino G, Burstein S and Di Marzo V: A structure-activity relationship study on N-arachidonoyl-amino acids as possible endogenous inhibitors of fatty acid amide hydrolase. Biochem Biophys Res Commun 314: 192-196, 2004.
86. Bachkangi P, Taylor AH, Bari M, Maccarrone M and Konje JC: Prediction of preterm labour from a single blood test: The role of the endocannabinoid system in predicting preterm birth in high-risk women. Eur J Obstet Gynecol Reprod Biol 243: 1-6, 2019.
87. Deutsch DG: A personal retrospective: Elevating anandamide (AEA) by targeting fatty acid amide hydrolase (FAAH) and the fatty acid binding proteins (FABPs). Front Pharmacol 7: 370, 2016.
88. Liu J, Bátkai S, Pacher P, Harvey-White J, Wagner JA, Cravatt BF, Gao B and Kunos G: Lipopolysaccharide induces anandamide synthesis in macrophages via CD14/MAPK/phosphoinositide 3-kinase/NF-kappaB independently of platelet-activating factor. J Biol Chem 278: 45034-45039, 2003.
89. Nagarkatti P, Pandey R, Rieder SA, Hegde VL and Nagarkatti M: Cannabinoids as novel anti-inflammatory drugs. Future Med Chem 1: 1333-1349, 2009.
90. Maccarrone M, Valensise H, Bari M, Lazzarin N, Romanini C and Finazzi-Agrò A: Relation between decreased anandamide hydrolase concentrations in human lymphocytes and miscarriage. Lancet 355: 1326-1329, 2000.
91. Dong C, Chen J, Harrington A, Vinod KY, Hegde ML and Hegde VL: Cannabinoid exposure during pregnancy and its impact on immune function. Cell Mol Life Sci 76: 729-743, 2019.
92. Hirota Y, Cha J, Yoshie M, Daikoku T and Dey SK: Heightened uterine mammalian target of rapamycin complex 1 (mTORC1) signaling provokes preterm birth in mice. Proc Natl Acad Sci USA 108: 18073-18078, 2011.
93. Wolfson ML, Aisemberg J, Correa F and Franchi AM: Peripheral blood mononuclear cells infiltration downregulates decidual FAAH activity in an LPS-Induced embryo resorption model. J Cell Physiol 232: 1441-1447, 2017.
94. Cox LS and Redman C: The role of cellular senescence in ageing of the placenta. Placenta 52: 139-145, 2017.
95. Singh M, Parent S, Leblanc V and Asselin E: Resveratrol modulates the expression of PTGS2 and cellular proliferation in the normal rat endometrium in an AKT-Dependent Manner1. Biol Reprod 84: 1045-1052, 2011.
96. Rajkovic J, Djokic V, Gostimirovic M, Gojkovic-Bukarica L, Martorell M, Sharifi-Rad J and Novakovic R: Potassium channels on smooth muscle as a molecular target for plant-derived Resveratrol. Cell Mol Biol (Noisy-le-Grand) 66: 133-144, 2020.
97. Carreiro JN, Magnani M, Jobling P, van Helden DF, Nalivaiko E and Braga VA: Resveratrol restores uterine contractions during hypoxia by blockade of ATP-sensitive potassium channels. J Funct Foods 33: 307-313, 2017.
98. Lim R, Barker G and Lappas M: Activation of AMPK in human fetal membranes alleviates infection-induced expression of pro-inflammatory and pro-labour mediators. Placenta 36: 454-462, 2015.
99. Novakovic R, Ilic B, Beleslin-Cokic B, Radunovic N, Heinle H, Scepanovic R and Gojkovic-Bukarica L: The effect of resveratrol on contractility of non-pregnant rat uterus: The contribution of K(+) channels. J Physiol Pharmacol 64: 795-805, 2013.
100. Okawa T, Longo M, Vedernikov YP, Chwalisz K, Saade GR and Garfield RE: Role of nucleotide cyclases in the inhibition of pregnant rat uterine contractions by the openers of potassium channels. Am J Obstet Gynecol 182: 913-918, 2000.

101. Brainard AM, Korovkina VP and England SK: Potassium channels and uterine function. Semin Cell Dev Biol 18: 332-339, 2007.
102. Zheng S, Feng Q, Cheng J and Zheng J: Maternal resveratrol consumption and its programming effects on metabolic health in offspring mechanisms and potential implications. Biosci Rep 38: BSR20171741, 2018.
103. Azachi M, Yatuv R, Katz A, Hagay Y and Danon A: A novel red grape cells complex: Health effects and bioavailability of natural resveratrol. Int J Food Sci Nutr 65: 848-855, 2014.
104. Wang P and Sang S: Metabolism and pharmacokinetics of resveratrol and pterostilbene. BioFactors 44: 16-25, 2018.
105. Pollack RM and Crandall JP: Resveratrol: Therapeutic potential for improving cardiometabolic health. Am J Hypertens 26: 1260-1268, 2013.
106. Shrikanta A, Kumar A and Govindaswamy V: Resveratrol content and antioxidant properties of underutilized fruits. J Food Sci Technol 52: 383-390, 2015.
107. Cione E, La Torre C, Cannataro R, Caroleo MC, Plastina P and Gallelli L: Quercetin, Epigallocatechin gallate, curcumin, and resveratrol: From dietary sources to human MicroRNA modulation. Molecules 25: 63, 2019.
108. Weiskirchen S and Weiskirchen R: Resveratrol: How much wine do you have to drink to stay healthy? Adv Nutr 7: 706-718, 2016.
109. Kuršvietienė L, Stanevičienė I, Mongirdienė A and Bernatonienė J: Multiplicity of effects and health benefits of resveratrol. Medicina (Kaunas) 52: 148-155, 2016.