

Review Article

A systematic review of the biological effects of resveratrol on venous thromboembolism

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Article history:

Received: Aug 25, 2024

Received in revised form:

Dec 23, 2024

Accepted: Dec 29, 2024

Epub ahead of print

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Keywords:

Resveratrol

Venous thromboembolism

Deep vein thrombosis

Pulmonary embolism

Thrombosis

Medicinal herbs

Abstract

Objective: Venous thromboembolism (VTE) has high morbidity in major surgery, serious injury, or during periods of inflammation and infection. VTE has serious complications, resulting in death. This review aims to evaluate the efficacy and mechanisms of resveratrol (RSV) in preventing and treating deep vein thrombosis (DVT) and pulmonary embolism (PE).

Material and methods: Various databases like MEDLINE/PubMed, Embase, Scopus, Cochrane Library, and Web of Science were comprehensively searched to find relevant studies published before January 2024. After defining the inclusion and exclusion, selecting studies related to the purpose of the study, data were extracted, and study characteristics, methods, and biological mechanisms were recorded and reviewed.

Results: RSV potentially prevents and attenuates VTE through antioxidant, anti-inflammatory, and anticoagulant mechanisms. It inhibited endothelial and platelet reactive oxygen species (ROS) production, enhanced endogenous antioxidants, and downregulated nuclear factor kappa B (NF-κB) and proinflammatory cytokines. RSV also regulated coagulation and fibrinolysis, inhibited tissue factor (TF) and myeloperoxidase (MPO), and reduced apoptosis. Additionally, RSV reduced adhesion molecule expression, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), P-selectin, and von Willebrand Factor (vWF), while promoting vasodilation and endothelial protection through increased nitric oxide (NO) production, SIRT1 activation, and ANGPT2 expression.

Conclusion: *In vivo* and *in vitro* studies have revealed that RSV has promising effects on DVT and PE. However, more well-designed controlled clinical trials with human subjects are needed to examine its application in clinical settings.

Please cite this paper as:

Momeni H, Shirvani-Farsani F, Baratpour I, Heidari-Soureshjani S, MT Sherwin C. A systematic review of the biological effects of resveratrol on venous thromboembolism. Avicenna J Phytomed, 2025. Epub ahead of print.

Introduction

Venous thromboembolism (VTE) is when blood clots form inside blood vessels, reducing blood flow (Hobohm et al. 2021). Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the leading causes of thrombosis mortality around the world (Stone et al. 2017). Venous thromboembolism can lead to leg swelling and sometimes post-thrombotic syndrome called DVT, and sometimes results in PE which can be life-threatening, and lead to chronic thromboembolic pulmonary hypertension. Moreover, VTE can occur in splanchnic veins and other unusual locations (Behravesht et al. 2017; Hong et al. 2021). In addition to causing considerable costs to the healthcare system, this disease causes work-related disability and untimely death in affected people (Braekkan et al. 2016; Bui et al. 2020). The treatment of VTE involves anticoagulation therapy. Usually, the standard VTE therapy includes warfarin or vitamin K-antagonists (VKAs), with heparin or fractionated heparin bridging. However, oral anticoagulants have been validated in certain cases to be used instead of warfarin, as per recent clinical trials carried out on a large scale (Hong et al. 2021; Stone et al. 2017). Bleeding, osteoporosis, and impaired renal function are most commonly associated with direct oral anticoagulant or VKA complications (Ageno and Donadini 2018; Martinez et al. 2020; Palareti et al. 2020). The increasing use of herbal medicines and phytopharmaceuticals as alternatives to conventional therapies for VTE highlights the growing demand for safer and more effective treatment options. This trend is particularly significant given the complications associated with widely used antithrombotic medications like warfarin and other oral anticoagulants (Mukherjee and Chattopadhyay 2022). Therefore, it is necessary to adopt effective and safe treatment strategies to treat thrombosis.

Recently, herbal remedies have gained popularity due to their lower side effects

compared to chemical drugs, affordability, detoxifying properties against cancer drugs, and promising outcomes in treating various diseases (Amini Chermahini et al. 2020; Ekor 2014; Jivad et al. 2024; Khaledifar et al. 2023). Resveratrol (RSV) is a polyphenol (trans-3,5,4'-trihydroxystilbene) found in nuts, grape, cassia and berries (Moshfegh et al. 2016; Wang et al. 2022). It has several beneficial properties including anti-inflammatory, antioxidant, and anti-tumorigenic effects (Bohara et al. 2022; Ramírez-Garza et al. 2018). Structurally, RSV belongs to the stilbenoid group which consists of two aromatic rings linked by an ethylene or ethene bridge (Roy et al. 2022).

In comparison to other phytochemicals that have antithrombotic properties, RSV rich diet is notable for its potential to interact with major pathways involved in thrombosis such as modulating the immune system and modulating inflammatory cytokines. Moreover, its favorable safety profile and well-documented efficacy in supporting cardiovascular health and vascular function further underscore its therapeutic potential (Berman et al. 2017; Gligorijević et al. 2021). In various studies, RSV have revealed cardioprotective, hepatoprotective, anticancer, and antiviral effects due to its antioxidant and anti-inflammatory effects (Izzo et al. 2021a; Planinc et al. 2022; Talib et al. 2020; Wang et al. 2022).

Considering the high morbidity and mortality associated with VTE and lack of a study to comprehensively review the efficacy and mechanisms of RSV in the treatment of VTE, the present systematic review study was designed and implemented.

Materials and Methods

Search strategy

To conduct an electronic search, we conducted a thorough systematic review on January 15, 2024, using high-coverage biomedical databases, such as

MEDLINE/PubMed, Embase, Web of Science (WOS), Cochrane Library, and Scopus. The primary and Medical Subject Headings (MeSH) keywords used for the electronic search were: ((“resveratrol” OR “3,4',5-Stilbenetriol” OR “3,4',5-Trihydroxystilbene” OR “3,5,4'-Trihydroxystilbene” OR “SRT 501”) AND (“thrombosis” OR “venous thrombosis” OR “deep vein thrombosis” OR “deep-vein thrombosis” OR “deep-venous thrombosis” OR “phlebothrombosis” OR “embolism” OR “pulmonary embolism” OR “thromboembolism” OR “pulmonary thromboembolism” OR “pulmonarythromboembolism”)). Searches were supplemented by a reference list review of relevant articles and studies from the prior review in this systematic review aim. The search was refined until all publications in the review were identified by our search. To ensure the accuracy of the research, we imported the peer-reviewed publications into EndNote 21.2 (released on October 17, 2023, by Thomson Reuters).

Selection criteria

All clinical and preclinical studies investigating the effects of RSV on VTE (including DVT and PE) in humans and animals were included. We selected clinical trials and observational studies that met the PICO (Patient/Population, Intervention, Comparison, and Outcome) criteria:

Population (P): Patients/animals/cells with DVT and PE, or those in experimental conditions where thrombosis is induced.

Intervention (I): Current treatment for VTE and RSV administration.

Control (C): Patients without thrombosis.

Outcomes (O): The primary mechanism of RSV in influencing thrombosis outcomes.

We excluded studies such as systematic reviews, meta-analyses, case reports, editorials, and reviews, articles did not have full-text availability, studies without original data, abstract-only publications, conference poster publications,

unpublished study protocols, studies published in languages other than English and letters to the editors.

Screening and full-text assessment

Two researchers independently reviewed the titles and abstracts of the studies using predefined inclusion and exclusion criteria. Publications that appeared to satisfy the inclusion criteria were listed, and their full-text versions were obtained for further evaluation. The same researchers then assessed the full texts to confirm eligibility. Any disagreements were resolved through discussion with a third reviewer.

Data extraction and narrative synthesis

The researchers reviewed full texts, and the most essential information related to the effect of RSV on DVT and PE was extracted. For each study, we recorded the first author's name, publication year, study setting, study design, models (participants/animals/cells), inducing thrombosis, dosage of RSV, and duration, registered in an Excel form.

Reporting guideline:

This systematic review is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Results

Search results

The process for searching relevant studies is shown in Figure 1 with PRISMA 2020 flow diagram. Initially, the electronic search detected 803 titles and abstracts. After removing 94 articles with duplicate titles, four titles, and abstracts were excluded for various reasons. Among these, one article was not published in English (Lou et al. 2018a), two were deemed irrelevant to the aim of this study (Huang et al. 2020; Pendurthi et al. 1999), and one because the full text was not available for review (WU and Chen 2016).

After careful evaluation and screening of articles, 20 studies were finally included, of which 11 were related to DVT (Banu et al. 2022; Fei et al. 2022; Kirimlioglu et al. 2008; Lou et al. 2017; Lou et al. 2018b; Lou et al. 2021; Lu et al. 2019; Shahidi et al. 2020; Xu et al. 2016; Yao et al. 2019; Zhang et al. 2018) and nine were related to PE (Chun et al. 2012; Dutra et al. 2017; Hsia et al. 2021; Huang et al. 2021; Kim et al. 2016; Lin et al. 2019; Liu et al. 2022; McCreary et al. 2022; Yang et al. 2019).

Description of the included studies

The studies were all preclinical, and only one study had a clinical trial design. Studies generally reported promising results from using RSV on VTE. The characteristics and consequences related to the effect of RSV on DVT are shown in Table 1, and the characteristics of the studies conducted regarding the mechanisms of RSV in reducing PE complications are shown in Table 2.

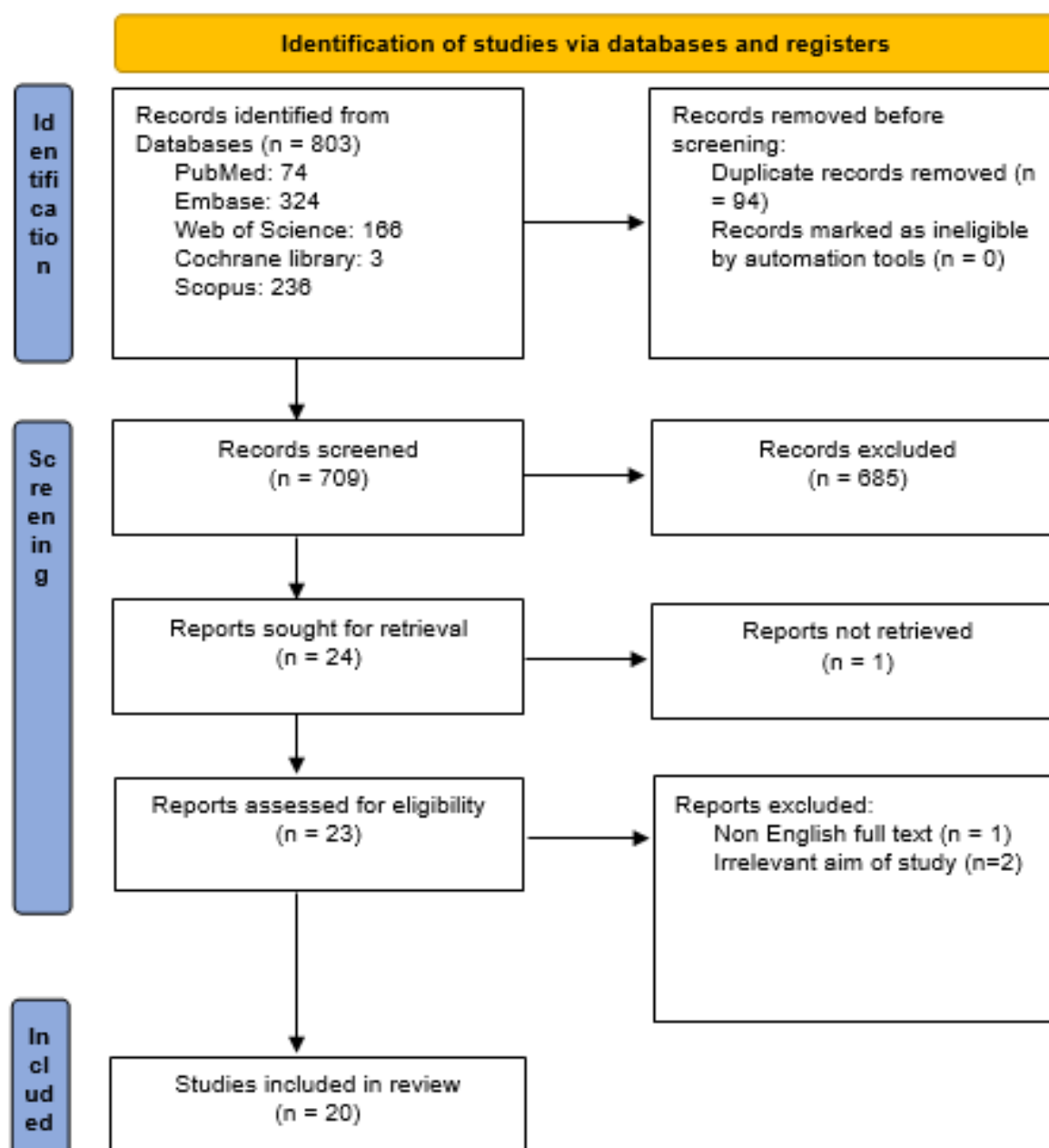


Figure 1. Flowchart for screening and including studies in the present systematic review

Antithrombotic effects of RSV

Table 1. Characteristics of the included studies that investigated the protective effects of RSV against DVT

Type of Study	Models (Patients, animals, cells)	Concentration, length of trial	Main mechanisms	The first author (Reference)
<i>In vivo</i>	Portal vein thrombosis in rats	60 mg/day of RSV was administered per nasogastric tube for ten days	↑ GSH ↓ MDA ⊥ Platelet aggregation and coagulation through creases in cAMP levels.	Kirimlioglu (Kirimlioglu et al. 2008)
<i>In vivo</i>	Fibrosis of male Sprague-Dawley rats induced by carbon tetrachloride	50 mg/day of RSV was administered per nasogastric tube for ten days	↓ Portal vein system thrombosis, platelet aggregation, and platelet ROS formation ↑ Platelet apoptosis and NO synthesis.	Xu (Xu et al. 2016)
<i>In vitro</i>	Human umbilical vein endothelial cells thrombosis-associated markers induced by H ₂ O ₂	30 μM of RSV for two hr	↓ P-selectin, PSGL-1, and vWF protein expression by H ₂ O ₂ via SIRT1 signaling.	Lou (a) (Lou et al. 2017)
<i>In vitro</i>	Human umbilical vein endothelial cells thrombosis-associated markers induced by H ₂ O ₂	0, 10, 20 and 30 μM of RSV for 2 hr	↓ ROS levels and suppression of the phosphorylated (p)-p38, P-c-JNKs, and P-ERK via inhibiting MAPK signaling pathways. ↓ Caspase-3, P-selectin glycoprotein ligand-1, and vWF expression.	Lou (b) (Lou et al. 2018b)
<i>In vivo, in vitro and ex vivo</i>	Endothelial progenitor cells and murine model of venous thrombosis	50 μM of RSV for 48 hr	↑ Thrombus resolution through attenuating miR-138 expression and, therefore, upregulated FAK.	Zhang (Zhang et al. 2018)
<i>In vivo and in vitro</i>	Rat model of venous thrombosis	25-75 μmol/L of RSV for two days	↑ Progenitor cells angiogenesis through decreased expression of miR-542-3p by targeting ANGPT2, enhanced thrombi recanalization.	Lu (Lu et al. 2019)
<i>In vivo and in vitro</i>	Male and female Sprague-Dawley rats with stenosis-induced DVT	25, 50, and 75 mg/kg of RSV once daily for two days	↓ The weight of blood clots, the number of white blood cells that entered the area of injury, the levels of two TNF-α and IL-1β, the levels of two proteins called Ace-p65 and TF. ↑ The levels of SIRT1 and its coding mRNA.	Yao (Yao et al. 2019)
<i>In vitro</i>	Thrombosis human umbilical vein endothelial cells	25, 50, and 100 mg/ml of RSV for 24-48 hr	↓ The levels of vWF, t-PA-1, IL-8, the activity of factor VIII, mRNA expression levels of Vwf, t-PA-1 and intracellular level of t-PA.	Shahidi (Shahidi et al. 2020)
<i>In vivo</i>	Thrombosis in DVT SAMP-1 mice model	20 mg/kg of RSV for 14 days	↓ The expression of p16, p21, mRNA, P-selectin, PSGL-1 and Vwf. ↑ P53 and acetylated p53 due to Sirt1 activation.	Lou (c) (Lou et al. 2021)
<i>In vivo and in vitro</i>	Ferric chloride-induced arterial thrombosis model in rats.	10-50 mg/kg/day of trans-RSV for 8-15 days	trans-RSV revealed antithrombotic and antiplatelet activities of some antioxidants	Banu (Banu et al. 2022)
<i>In vivo</i>	Sprague-Dawley rats with inferior vena cava thrombosis.	15-60 mg/kg for 1 hr	↓ Lesions in the IVC and lung tissue, thrombosis, the levels of D2D, F1 + 2, caspase-1, IL-1β, TF, NLRP3 and HIF-1α	Fei (Fei et al. 2022)

↑, Increase; ↓, Reduce; ⊥, Inhibit; RSV, Resveratrol; DVT, Deep vein thrombosis; cAMP, Cyclic adenosine monophosphate; ROS, Reactive oxygen species; NO, Nitric oxide; SIRT1, Silent mating type information regulation two homolog1; GSH, Glutathione; MDA, Malondialdehyde; PSGL-1, P-selectin glycoprotein ligand-1; vWF, von Willebrand factor; MAPK, Mitogen-activated protein kinase; TF, Tissue Factor; ERK, Extracellular signal-regulated kinase; JNKs, Jun N-terminal kinases; FAK, Focal adhesion kinase; ANGPT2, Angiotensinogen; TNF-α, Tumor necrosis factor-α; IL, Interleukin; mRNA, Messenger ribonucleic acid; t-PA-1, Tissue plasminogen activator-1; D2D, D-dimer; F1 + 2, Prothrombin fragment 1 + 2; NLRP3, NOD-like receptor protein 3; IVC, Inferior vena cava.

Table 2. Characteristics of the included studies that investigated the protective effects of RSV against PE

Type of Study	Models (Patients, animals, cells)	Concentration, length of trial	Main mechanisms	The first author (Reference)
<i>In vivo and in vitro</i>	Male Sprague–Dawley adult rats induced PTE by infusion of an autologous blood clot into the pulmonary artery	10 mg/kg/day, i.p of RSV for 1-8 hr	↓ Formation of PTE through down-regulation of the MCP-1 expression by suppressing acute PTE-induced p-p38MAPK activation.	Chun (Park et al. 2012)
<i>In vivo and in vitro</i>	PE was induced by PAF, AA, ADP, and thrombin in SIRT1-transgenic mice (C57BL/6N) w	Ten μ M for one hr of RSV administered to mice (95 μ g/kg) or a combination of NAM (5 μ g/kg) + RSV (same dose)	↑ SIRT1 ↓ PAFR expression on platelets by proteasomal and lysosomal pathways, ⊥ Platelet aggregation <i>in vitro</i> and PE formation <i>in vivo</i> .	Kim (Kim et al. 2016)
<i>In vivo and in vitro</i>	Mouse pulmonary thromboembolism model induced by ADP	150 μ M compounds of RSV (2a–f and 4a–f)	⊥ Platelet aggregation by releasing NO agonists ADP, collagen, and arachidonic acid.	Dutra (Dutra et al. 2017)
<i>In vivo and in vitro</i>	In male Sprague-Dawley adult rats, acute PTE was established in the pulmonary artery)	10 mg/kg/day, i.p. of RSV for 1-8 hr	⊥ TNF- α -induced p-p38MAPK expression through down-regulating MCP-1 expressions of RPAs-RSV.	Lin (Lin et al. 2019)
<i>In vivo, in vitro and in-silico</i>	Male Sprague-Dawley rats with cardiac injury induced by PE	30 mg/kg of RSV and followed for six weeks	↓ MALAT1/NLRP3 and miR-22-3p expression (following its direct target) ⊥ ASC, caspase-1, IL-1 β , and IL-18	Yang (Yang et al. 2019)
<i>In vivo and in vitro</i>	Intravenous injection of ADP in experimental mic and washed human platelets	Pterostilbene at 2 mg/kg was administered	⊥ Platelet aggregation, IKK and p65 phosphorylation. ↓ NF- κ B signaling pathway, and MK-2206 (an inhibitor of Akt)	Hsia (Hsia et al. 2021)
<i>In vivo and in vitro</i>	ADP-induced acute pulmonary thromboembolism in male ICR mice using the tail-vein transection model	1–100 μ mol/L of pterostilbene in platelets for 20 min and 0.6 and 1.2 mg/kg PTE in mice	↓ P-selectin expression on isolated α -granules, inhibited collagen-activated platelets, PLC γ 2/ PKC, and MAPK phosphorylation. ⊥ ATP production and intracellular ([Ca ²⁺] _i) mobilization.	Huang (Huang et al. 2021)
<i>In vivo and in vitro</i>	Male Sprague Dawley rats with autologous blood clots, pulmonary embolism, and Human Pulmonary Artery Endothelial Cells.	RSV at 10 mg/kg/day concentration for 1, 2, and 4 weeks in rats and 5, 10, or 20 μ M in cells	↑ Thrombolysis and pulmonary artery function, reducing mPAP and WA/TA. ⊥ IL-6, IL-1 β , MPO, TF, vWF, P-selectin, promote SOD in plasma, MCP-1, Ac-FOXO1, VCAM-1, ICAM-1, caspase 3 and 9, and Bax.	Liu (Liu et al. 2022)
RCT	COVID-19 patients	RSV administered two capsules four times per day for at least 7-15 days	Pulmonary embolism incidence rates were equal in both studied groups.	McCreary (McCreary et al. 2022)

↑, Increase; ↓, Reduce; ⊥, Inhibit; RSV, Resveratrol; PE, Pulmonary embolism; PTE, Pulmonary thromboembolism; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte chemoattractant protein-1; p-p38MAPK, phosphorylation of p38 MAPK; SIRT1, Silent mating type information regulation two homolog1; PAFR, Platelet-activating factor receptor; AA, Arachidonic acid; ADP, Adenosine diphosphate; NO, Nitric oxide; TNF- α , Tumor necrosis factor-alpha; ASC, Apoptosis-associated speck-like protein containing a caspase recruitment domain; IL, Interleukin; ATP, Adenosine triphosphate; PLC, Phospholipase C; NF- κ B, Nuclear factor kappa B; IKK, I κ B Kinase; PKC, Protein kinase C; TF, Tissue Factor; mPAP, Mean Pulmonary Arterial Pressure; WA/TA, vessel Wall Area/ Total Area; vWF, von Willebrand factor; SOD, Superoxide dismutase; MPO, Myeloperoxidase; Ac-FOXO1, (A) Immunoblotting for FoxO1 and acetylated FoxO1; VCAM-1, Vascular cell adhesion protein 1; ICAM, Intercellular adhesion molecule; RCT, Randomized clinical trial; NLRP3, NOD-like receptor protein 3.

Discussion

This systematic review investigated the effects of RSV on VTE, focusing on the mechanisms as follows:

Antioxidant effects

Oxidative stress is a complex phenomenon when the generation of reactive oxygen species (ROS) surpasses the body's ability to detoxify or repair the damage (Pizzino et al. 2017). Studies have demonstrated that polyphenols provide beneficial effects by decreasing endothelial dysfunction, platelet activation, oxidative stress in the vascular wall, over activity of the local angiotensin system, and heightened prothrombotic reactions due to cardiovascular diseases (Oak et al. 2018; Tromba et al. 2019). It has been proposed that oxidative stress may contribute to thrombotic events through several mechanisms.

Oxidative stress and inflammation significantly impact the endothelial cells, shifting their function from a vasoprotective, prothrombotic, and pro-apoptotic state to a vasoconstrictive one (Drożdż et al. 2023). ROS significantly reduces nitric oxide (NO) production while oxidative stress, inflammation, and endothelial dysfunction exacerbate the damaging process (Gaur et al. 2024). In this regard, an *in vivo* study, conducted by Xu et al., revealed that 50 mg/day of RSV administration through nasogastric tube for ten days in fibrosis of male Sprague-Dawley rats induced by carbon tetrachloride could reduce portal vein system thrombosis, platelet ROS formation, and improved platelet NO synthesis (Xu et al. 2016). Another study by Lou et al. reported that applying 30 μ M of RSV for two hr on human umbilical vein endothelial cells thrombosis-associated markers induced by H₂O₂ could downregulate thrombosis-associated markers through reduced ROS levels (Lou et al. 2018b). Prooxidant stimulants such as ROS, angiotensin II, Endothelin-1 (ET-1), and inflammatory cells tend to dominate the

antioxidant defense and can lead to oxidative stress (Cushnie et al. 2024). This stress triggers inflammation, which results in endothelial dysfunction and vascular tone regulation impairment. Furthermore, it increases the susceptibility to forming foam cells and adverse vascular remodeling (D'Oria et al. 2020; Guo et al. 2014; Moris et al. 2017).

Moreover, oxidative stress has been linked to increased platelet activation and aggregation which are critical players in the formation of blood clots. Elevated ROS levels may enhance platelet reactivity, promoting thrombus formation. Oxidative stress may also influence the activation of various coagulation cascade components including clotting factors and fibrinolysis, and involve various cell types and anticoagulant pathways (Bettiol et al. 2022; Wang and Zennadi 2020). The intricate interplay between ROS and mitochondria is the critical regulator of platelet functions. A profound shift in platelets' redox balance and metabolism occurs upon activation. Upon activation, multiple signaling pathways stimulate the production of ROS by NADPH oxidase (NOX) and mitochondria. These ROS molecules derived from platelets, act as a catalyst, further amplifying the production of ROS and triggering a self-propagating loop of platelet activation, adhesion, and recruitment (Masselli et al. 2020).

Furthermore, the accumulation of ROS within red blood cells (RBCs) is caused by the constant autoxidation of endogenous hemoglobin (Hb) and trigger of NADPH oxidase, as well as the absorption of extracellular ROS formed by other cells in circulation. This accumulation can increase RBC ROS levels, ultimately affecting the structure and function of the RBC membrane (Wang and Zennadi 2020). Abnormal erythrocytes, also known as RBC, which are present in certain medical conditions, tend to attach to the inner lining of blood vessels. This attachment can contribute to generation of thrombin, a protein involved in blood clotting, and

formation of a thrombus, or blood clot. Such a process can lead to an accelerated breakdown of RBC, a condition known as hemolysis, and a hypercoagulable state where the blood has an increased tendency to clot (Bettioli *et al.* 2022).

Antioxidant enzymes play a critical role in protecting our bodies from the harmful effects of unstable molecules, also known as free radicals. These enzymes compromise glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT). SOD and CAT, in particular, act as the primary defense system against free radicals by neutralizing two of the most common types of ROS, including O₂⁻ and hydrogen peroxide (H₂O₂). This process of scavenging ROS is vital for maintaining the delicate balance of our cells and preventing oxidative stress (Pham-Huy *et al.* 2008). On the other hand, when a tissue is subjected to oxidative stress due to the presence of H₂O₂, it can cause changes in the activities of CAT, GPx, NO synthase, and its levels. However, it has been found that RSV treatment can help prevent these changes (Konyalioglu *et al.* 2013). Kirimlioglu *et al.* (Kirimlioglu *et al.* 2008) and Liu *et al.* (Liu *et al.* 2022) in their studies indicated that 60 mg/day of RSV was administered per nasogastric tube for ten days and 10 mg/kg/day of RSV concentration for 1, 2, and 4 weeks in rats respectively can increase GSH and decrease MDA and SOD in plasma.

Moreover, RSV is considered a Sirtuin 1 (SIRT1) activator. The primary responsibility of SIRT1 is to respond to oxidative stress by regulating several transcription factors, including forkhead box protein O1 (FOXO1), FOXO3a, FOXO4, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and nuclear factor kappa B (NF-κB) regulators. These transcription factors work in concert to activate the expression of antioxidant enzymes and eliminate ROS (Gu *et al.* 2021).

A study indicated that 30 μM of RSV has been found to have a promising effect on

venous thrombosis. It can reduce the activation of thrombosis-related markers caused by H₂O₂ by activating SIRT1, a protein that plays a crucial role in cellular metabolism and stress response (Lou *et al.* 2017).

Lastly, oxidative stress might influence the composition and stability of blood clots, given the changes in the redox state within the thrombus, which may affect its susceptibility to lysis and resolution (Izzo *et al.* 2021b).

Oxidative stress which leads to increased levels of ROS, is vital in altering the extracellular matrix (ECM) turnover and metabolism. The ECM is responsible for providing structural support to the cells and tissues. Any disturbance in its balance can lead to various pathological conditions. In human aging hearts with atrial fibrillation, matrix metalloproteinase (MMP) levels, a family of enzymes involved in ECM degradation, are significantly elevated (Zhan *et al.* 2018).

Anti-inflammatory effects

Inflammation plays a complex role in the pathophysiology of DVT and PE, involving multiple mechanisms. The close relationship between inflammation and thrombosis is essential for containing the spread of pathogens through immunothrombosis. However, excessive activation or dysregulation of this mechanism can lead to thromboinflammation which causes tissue ischemia due to thrombi formation (Marcos-Jubilar *et al.* 2023).

The main factor behind these processes is the vicious cycle of platelet and innate immune cell activation, complement system, and coagulation cascade. Clinical evidence supports the connection between inflammation and thrombosis, as various conditions such as chronic autoimmune diseases, infections, and hematopoiesis of indeterminate potential, are associated with a higher risk of thrombotic events (Stark and Massberg 2021).

Inflammation and oxidative stress are also interconnected, where oxidative stress can trigger inflammatory responses, and inflammation, in turn, can contribute to oxidative stress. Chronic inflammation, a risk factor for DVT and PE, may be influenced by oxidative stress (Siti et al. 2015).

Numerous intracellular pathways are known to be activated in endothelial cells, leading to phenotypical changes that impart an inflammatory cell-like appearance.

Recent evidence suggests that endothelial-to-mesenchymal transition (EndMT) plays a crucial role in endothelial dysfunction associated with inflammation and thrombosis (Pilard et al. 2022). In response to growth factors and cytokines such as thrombin, tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and insulin, an increase in ET-1 synthesis is also observed.

Similarly, vasoactive substances including norepinephrine, angiotensin II, vasopressin, and bradykinin also increase ET-1 synthesis (Genovesi et al. 2022). Elevated ET-1 and platelet-activating factor (PAF) synthesis leads to vasoconstriction and enhances the prothrombotic state (Gross and Aird 2000). Additionally, Increased levels of C-reactive protein (CRP), IL-6, IL-8, and TNF- α during systemic inflammation have been associated with a higher risk of VTE (Branchford and Carpenter 2018; Poredos and Jezovnik 2007). *In vitro* and *in vivo* studies investigating RSV effects on proinflammatory cytokines have shown that RSV can reduce IL-8, IL-1 β , and IL-18 in DVT and PE situations (Shahidi et al. 2020; Yang et al. 2019). An *in vivo* and *in vitro* study by Yao et al. demonstrated that administration of 25 mg/kg of RSV once daily for two days in male and female Sprague–Dawley rats with stenosis-induced DVT can decrease the number of white blood cells that entered the area of injury, and lower the levels of two TNF- α and IL-1 β (Yao et al. 2019). Another study indicated that administration of 10

mg/kg/day of RSV for 1-8 hr in male Sprague–Dawley adult rats with acute PE could inhibit TNF- α -induced p-p38MAPK expression through downregulation of monocyte chemoattractant protein-1 (MCP-1) (Lin et al. 2019). The NF- κ B pathway which regulates proinflammatory cytokine production, was inhibited by Pterostilbene (natural polyphenol and a stilbenoid chemically related to RSV) at 2 mg/kg administration in rats (Hsia et al. 2021).

The nucleotide-binding domain leucine-rich repeat-containing protein 3 (NLRP3) inflammasome plays a fundamental role in producing and maturing IL-1 β , a proinflammatory cytokine. It requires the integration of two distinct signals. The initial priming signal triggers the transcription and translation of NLRP3 and pro-IL-1 β via a signaling cascade involving the Toll-like receptor-nuclear factor-kappa B (TLR-NF- κ B) pathway (Lebreton et al. 2018). Fei et al. reported that 60 mg/kg of RSV for 1 hr in Sprague–Dawley rats with inferior vena cava thrombosis could reduce the expression of NLRP3 and hypoxia-inducible factor-1 α (HIF-1 α) (Fei et al. 2022). Another study indicated that 30 mg/kg of RSV, after six weeks, reduced MALAT1/NLRP3 and miR-22-3p expressions (Yang et al. 2019).

Monocyte chemoattractant protein-1 (MCP-1) is also a potent inflammatory cytokine associated with thrombosis formation (Chen et al. 2020). Studies suggest that measuring plasma levels of MCP-1 can provide valuable prognostic information in cardiac diseases and might be considered independent of standard clinical variables. MCP-1 may have prothrombotic effects, increasing the risk of DVT and PE (Gonzalez-Quesada and Frangogiannis 2009; Humphries et al. 1999). Two *in vivo* and *in vitro* studies by Chun et al. and Lin et al. indicated that 10 mg/kg/day, intraperitoneal (i.p) of RSV for 1-8 hr in male Sprague–Dawley adult rats acute PE inhibited TNF- α -induced p-p38MAPK expression through

downregulating MCP-1 expressions of rat pulmonary artery endothelial cells (RPAs)-RSV (Lin et al. 2019; Park et al. 2012).

The coagulation system can be activated by induction of tissue factor (TF) by activating endothelial cells, platelets, and leukocytes, which then form microparticles (Branchford and Carpenter 2018). The activation of TF has been demonstrated to elicit a clotting response in venous thrombosis. Furthermore, the presence of inflammation exacerbates TF activity in triggering exogenous coagulation pathways, thereby resulting in the formation of extensive fibrin in venous vessels (Müller et al. 2003). Liu et al. reported that RSV at 10 mg/kg/day promoted thrombolysis and pulmonary artery function by inhibiting TF in male Sprague Dawley rats with autologous blood clots and pulmonary embolism (Liu et al. 2022). RSV at 60 mg/kg in Sprague–Dawley rats with inferior vena cava thrombosis could attenuate lesions in the inferior vena cava lung tissue and the thrombosis was attenuated in the RSV group by reducing TF (Fei et al. 2022). Yao et al. revealed that the administration of 25 mg/kg of RSV once daily for two days in male and female Sprague-Dawley rats with stenosis-induced DVT decreased the number of white blood cells that entered the area of injury and lowered the levels of two proteins called Ace-p65 and TF (Yao et al. 2019).

In addition, inflammation can recruit neutrophils and lead to the formation of neutrophil extracellular traps (NETs), contributing to thrombus formation (Zhou et al. 2021). Neutrophils and NETs play a critical role in the formation of thrombosis. Upon being stimulated by pathogens, neutrophils release extracellular structures known as NETs. These structures contain active substances such as neutrophil elastase (NE), myeloperoxidase (MPO), and cathepsin G. NETs form a network structure that can prevent the spread of pathogens, effectively killing and eliminating them. However, the

components of NETs can also activate the coagulation pathway abnormally, contributing to the formation of pathological thrombus (Zhou et al. 2022). NETs are complex structures that play a crucial role in developing DVT. These specialized formations are released by neutrophils, which can effectively capture harmful pathogens and facilitate clotting within the body's deep veins (Yao et al. 2023).

According to recent studies, an imbalance in the vascular microenvironment and the overproduction of NETs can result in abnormal thrombosis. NETs serve as a structure for platelets, RBCs, and coagulant molecules, which can lead to thrombosis. Additionally, the protein constituents found in NETs can activate the body's natural coagulation process, ultimately leading to thrombosis. Therefore, NETs are essential in developing arterial, venous, and cancer-related thrombosis (Zhou et al. 2021). In thrombosis formation, the von Willebrand Factor (vWF) plays a crucial role in preserving DNA and elevating serum DNA levels.

Consequently, specific markers of NETs, such as extracellular DNA and citrullinated histone H3 (CitH3), may be present within the thrombus (El-Sayed et al. 2016). Research has shown that Monocyte Extracellular Traps (ETs) have a similar structure to NETs and contain substances such as MPO, lactoferrin, citrullinated histones, and elastase, which can increase the risk of clotting (Granger et al. 2017). Exosomal MPO, considered a biomarker of DVT, increased sharply in animals with inferior vena cava ligation (Han et al. 2022). Another study indicated that RSV promoted thrombolysis and pulmonary artery function by inhibiting MPO in male Sprague Dawley rats with autologous blood clots and pulmonary embolism (Liu et al. 2022).

Caspase-1 is an enzyme present in different cell types, including immune and non-immune cells. When activated, it

triggers the formation of gasdermin D, which acts as a protein channel or pore that allows the release of cytokines IL-1 β and IL-18. These cytokines are essential in the body's immune response and inflammatory processes (Yang et al. 2019). Caspase-1 is thought to primarily regulate cell death and protein secretion while potentially affecting lysosomal function that varies depending on the specific cell type (Molla et al. 2020). Administration of 30 mg/kg of RSV for six weeks resulted in a significant reduction in the expression levels of caspase-1, IL-1 β , and IL-18, indicating its potential anti-inflammatory effects (Yang et al. 2019).

Inflammatory mediators can also downregulate natural anticoagulant pathways, exacerbating the risk of thrombotic events. When exposed to endotoxin and inflammatory agents, endothelial cells are prompted to express TF and factor XII. This leads to the activation of the coagulation pathway and consumption of natural coagulation inhibitors like antithrombin III, protein C, and protein S (Landau et al. 2022; van Hinsbergh 2012).

Anti-apoptosis effects

Thrombi form when specific coagulation factors such as fibrinogen and factor XIIa, are triggered on biomaterials in conjunction with TF from inflammatory cells like neutrophils and monocytes. The process of platelet activation leads to the conversion of native CRP into monomeric C-reactive protein (mCRP). In addition, microparticles generated by apoptotic and activated cells and platelets can separate native CRP into mCRP and contain TF. When cells are present in the bloodstream, they attach themselves to protein surfaces and enter the biomaterial, producing MMPs and ROS and triggering inflammation (Labarrere et al. 2020). So, proinflammatory stimuli, such as TNF- α , CRP, TF, and interferon-gamma (IFN- γ), may compromise cell survival pathways in monocytes, endothelial cells, and platelets (Affara et al. 2007; Mallat and Tedgui 2000; Nan et al.

2023). Therefore, these inflammatory and oxidative pathways precipitate apoptotic trends during VTE.

Moreover, the balance of endothelial cell growth and decay is essential for creating new vessels and the regression of preexisting ones during both normal development and disease (Mallat and Tedgui 2000). The connection between cells via the VE-cadherin pathway is crucial for the survival of growth factors such as vascular endothelial growth factor (VEGF). Shear stress can increase the level of VE-cadherin expression. The process of Akt phosphorylation plays a crucial role in several signaling pathways associated with anti-apoptotic effects, which in turn affect the equilibrium between pro-apoptotic and anti-apoptotic members of the bcl-2 family (Mallat and Tedgui 2000; Nan et al. 2023).

Lou et al. demonstrated that treatment with 30 μ M of RSV on human umbilical vein endothelial cells, which were exposed to H₂O₂ for 2 hours and associated with thrombosis markers, inhibited the phosphorylation of p38, c-Jun N-terminal kinases (c-Jun) and extracellular signal-regulated kinases (ERK). This effect was attributed to the inhibition of the MAPK signaling pathways (Lou et al. 2018b). P53 can induce apoptosis in cells commonly by direct transcriptional activation of the pro-apoptotic pathways (Lebreton et al. 2018). In Lou et al. study (Lou et al. 2021), RSV reduced the expression of p16 and p21 and increased p53 and acetylated p53 due to SIRT1 activation by administration of 20 mg/kg of RSV for 14 days in thrombosis in the DVT SAMP-1 mice model. Moreover, the application of RSV in male Sprague Dawley rats with autologous blood clot-induced PE inhibited caspase-3, caspase-9, and Bcl-2-associated X protein (BAX) (Liu et al. 2022).

Anticoagulation and antiplatelet activity

The coagulation system is critical in developing VTE.

The initiation of the coagulation cascade is a complex process that involves several

pathways and mechanisms. Typically, coagulation is initiated in response to vascular injury or activation. When blood vessels are damaged, tissues release TF, a vital initiator of the extrinsic coagulation pathway. The extrinsic pathway is triggered by TF, forming a complex with factor VII which activates factors IX and X, leading to the conversion of prothrombin to thrombin. Simultaneously, the intrinsic pathway is activated within the bloodstream, involving factors XII, XI, IX, and VIII (Palta et al. 2014). As age develops, there is typically a gradual increase in the concentration of specific coagulation factors found in plasma, including factor V, VII, VIII, IX, and fibrinogen. A similar trend is observed with vWF, a vital protein responsible for the interaction between platelets and the walls of blood vessels. The elderly population has a greater risk of cardiovascular events, which could be related to higher levels of plasma fibrinogen (Franchini 2006). This protein aids in platelet bridging through the glycoprotein IIb-IIIa receptor and is a direct substrate for clotting. Moreover, the elevated levels of fibrinogen can lead to an increase in blood viscosity and thrombosis (Previtali et al. 2011). Shahidi et al. indicated that 25, 50, and 100 mg/ml of RSV for 24-48 hr on thrombosis in human umbilical vein endothelial cells attenuated the levels of vWF and t-PA-1 as well as the activity of factor VIII (Shahidi et al. 2020).

The coagulation cascade involves thrombin as a key enzyme which facilitates the conversion of fibrinogen to fibrin. Fibrin forms a mesh that helps in stabilizing the blood clot. Platelets play a crucial role in developing VTE, as they are activated and aggregated together to form a plug at the site of vascular injury. Activated platelets also provide a surface for the coagulation cascade, facilitating the conversion of prothrombin to thrombin (Vrotniakaite-Bajerciene et al. 2023). Fibrin strands generated by thrombin weave through the platelet plug, forming a stable blood clot. This process, known as

secondary hemostasis, reinforces the initial platelet plug and prevents bleeding. While the coagulation system promotes clot formation, anticoagulant mechanisms act to prevent excessive coagulation. Fibrinolysis breaks down fibrin clots, which helps prevent clot propagation and promotes clot resolution (Periayah et al. 2017). Certain genetic and acquired conditions can lead to a hypercoagulable state, making individuals more prone to thrombosis. Venous stasis, or slow blood flow, is a risk factor for DVT, and if a clot in the deep veins dislodges and travels to the lungs, it can cause a PE, obstructing blood flow. Moreover, D-dimer (D2D) and prothrombin fragment 1+2 (F1+2) levels were reduced following the administration of 15–60 mg/kg of RSV treatment for one hour in Sprague–Dawley rats with inferior vena cava thrombosis (Fei et al. 2022).

Platelets play a crucial role in the interplay between thrombosis and inflammation, two essential aspects of hemolysis-associated disorders. Platelets require pattern recognition receptors, such as toll-like receptor 4 (TLR4) and NLRP3 (Vogel and Thein 2018), to fulfill this role. NLRP3 forms multiprotein inflammasome complexes within platelets.

Additionally, platelets are susceptible to damage-associated molecular pattern (DAMP) molecules such as free haem and high-mobility group box 1 (HMGB1), which can target and affect them. HMGB1 is a DNA-binding protein, released by activated platelets and dying or stressed cells, while free haem is a by-product occurring during hemolysis from Hb oxidation. Platelet TLR4, NLRP3, and Bruton tyrosine kinase (BTK) play a crucial role in regulating platelet aggregation and thrombus formation (Vogel and Thein 2018).

Adhesion molecules

Another mechanism contributing to VTE is leukocyte adhesion and infiltration, which is facilitated by the expression of adhesion molecules on endothelial cells.

Leukocytes can release proinflammatory factors, contributing to forming a prothrombotic environment (Yao et al. 2023).

Specific proteins including vascular cell adhesion molecule-1 (VCAM-1), P-selectin, complement components, and fibrinogen, can adhere to biomaterials circulating in the body. This protein adhesion promotes the attachment of neutrophils and macrophages to the biomaterial. Macrophages use various integrins on their surfaces to attach to protein-coated biomaterials like vitronectin, fibronectin, Factor Xa, fibrinogen, complement components, and other inflammatory cell surfaces (Labarrere et al. 2020). Liu et al. in their study showed that RSV administration (10 mg/kg/day concentration) in rats inhibited MCP-1, Ac-FOXO1, VCAM-1, intercellular adhesion molecule 1 (ICAM-1) (Liu et al. 2022).

Neutrophils are the most prevalent leukocyte found in venous thrombosis. While they can contribute to damage in the vein walls, they also serve a vital role in regulating the production and activity of fibrinolytic enzymes, promoting the breakdown of fibrin and collagen, and are essential for early thrombus lysis (Longstaff and Kolev 2015). Plasmin is a crucial component of thrombolysis, particularly in the early stages of venous thrombolysis. Meanwhile, D-dimer is a degradation product of fibrinolysis that is clinically significant due to its ability to diagnose, assess efficacy, and predict prognosis in cases of thrombotic disease. Additionally, neutrophils can secrete MMP, activating the plasminogen activation system and reducing the accumulation of inflammatory factors in DVT formation (Yao et al. 2023).

Moreover, following blood vessel injury, platelets adhere to exposed collagen at the injury site and become activated, releasing adenosine diphosphate (ADP) and thromboxane A₂ (TXA₂). These molecules act as potent platelet agonists, amplifying platelet recruitment and aggregation to

form a hemostatic plug, effectively inhibited the bleeding (Caillon et al. 2022). Platelets and RBCs are the primary components of a thrombus which can form in a flowing or static blood environment. After a few days, inflammatory cells such as neutrophils, lymphocytes, and monocytes, infiltrate the margins of the thrombus, leading to an inflammatory response. This process depends on endothelial activation and can increase the expression of cell adhesion molecules, including p-selectin, e-selectin, and vWF (Ley et al. 2007).

The P-selectin/PSGL-1 pathway is also responsible for critical events in starting and spreading venous thrombosis. It makes it easier for leukocytes and platelets to accumulate within the growing thrombus. Both activated platelets and endothelium contain P-selectin and bind to P-selectin glycoprotein ligand-1 (PSGL-1) in all leukocytes (Wong et al. 2021). A highly potent P-selectin inhibitor called PEG40-GSnP-6 (P-G6) has been created to counter this. P-G6 has been shown to inhibit platelet-monocyte and platelet-neutrophil aggregation *in vitro* and blocks microcirculatory platelet-leukocyte interactions *in vivo* (Wong et al. 2021). Studies have shown that 10, 20, and 30 μ M of RSV for 2 hr attenuated P-selectin and glycoprotein ligand-1, PSGL-1, and vWF protein expression (Liu et al. 2022; Lou et al. 2017; Lou et al. 2018b; Lou et al. 2021; Shahidi et al. 2020).

Vasodilation and endothelial protection

Various factors have important roles in PE and DVT incidence, including activated platelets, endothelial effects, reflexes, and hypoxia. This interaction leads to vasoconstriction (Lyhne et al. 2020). NO primarily induces vasodilation through the endothelial NO synthase (eNOS)/NO/cyclic guanosine monophosphate (cGMP) pathway activity. This pathway is the primary mechanism through which, NO exerts its vasodilatory effects. In the glomeruli, eNOS is

predominantly expressed in the endothelial cells, crucial in regulating blood flow (Ahmad et al. 2018). When NO binds to soluble guanylate cyclase (sGC), it activates the enzyme and triggers the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).

In two *in vivo* and *in vitro* studies, RSV improved platelet apoptosis and NO synthesis and released NO agonists ADP (Dutra et al. 2017; Xu et al. 2016).

RSV has potential cardiovascular benefits, including vasodilation and endothelial protection, that may reduce the risk of VTE (Gal et al. 2021). RSV enhances NO synthesis in endothelial cells, a potent vasodilator that relaxes vascular smooth muscle cells, leading to increased blood flow and improved endothelial function. It activates eNOS, the enzyme responsible for NO production in endothelial cells, and supports NO generation, contributing to vasodilation (Li et al. 2019). RSV-induced NO production may enhance the cGMP pathway by activating SIRT1 which leads to the relaxation of vascular smooth muscle, contributing to vasodilation (Fukuhara et al. 2011). RSV has been shown to decrease the production of ET-1, a vasoconstrictor, which may contribute to vasodilation and prevent excessive vasoconstriction. RSV may improve overall endothelial function by supporting the production of vasodilators, reducing vasoconstrictors, and enhancing antioxidative defense mechanisms (Gordish and Beierwaltes 2014; Li et al. 2019).

RSV modulates calcium channels by directly inhibiting the L-type voltage-gated calcium channels (VGCC), which influences intracellular calcium levels, affecting smooth muscle contractility and promoting vasodilation (McCalley et al. 2014). It also activates potassium channels, leading to cell membrane hyperpolarization, reducing smooth muscle cell excitability, and contributing to vasodilation. RSV primarily targets the

plasma membrane. It also indirectly affects the large conductance calcium-activated potassium (BK) channel, improving the endothelium and vascular function (Protić et al. 2013).

Furthermore, angiopoietin-2 (ANGPT2) is a protein that plays a crucial role in regulating the formation of new blood vessels (angiogenesis) and the resolution of blood clots in veins. However, when ANGPT2 is overproduced, it can lead to the development of thrombo-fibrosis, a condition characterized by the formation of fibrous tissue within blood clots (Hobohm et al. 2021). EPCs were treated with 25 µmol/L of RSV for 2 days. The presence of miR-542-3p led to a reduction in luciferase activity. Furthermore, results from western blot and RT-PCR analyses demonstrated that miR-542-3p affected the expression of ANGPT2 at the post-transcriptional level (Lu et al. 2019).

Activating SIRT1

SIRT1, belonging to the sirtuin family of NAD⁺-dependent deacetylases, has been found to play a crucial role in various cellular processes such as metabolism, stress response, and aging (Bettioli et al. 2023). Studies have shown that Sirt1, a protein that regulates gene expression, is connected to various medical conditions, including inflammation, oxidative stress, platelet adhesion, and endothelial cell senescence (Huang et al. 2023; Lou et al. 2021; Pan et al. 2022). SIRT1-AS, a type of RNA that works in opposition to SIRT1, is a crucial factor in developing DVT due to its association with decreased SIRT1-AS and SIRT1 lncRNA expression. By slowing down aging and reducing the likelihood of blood clot formation, SIRT1 plays a vital role in preventing DVT. Additionally, the SIRT1-AS antisense RNA helps to reduce the risk of DVT by regulating the SIRT1/FOXO3a pathway (Huang et al. 2023; Lou et al. 2021). SIRT1 is crucial in regulating thrombosis and modulating key pathways like endothelial activation, coagulation, and platelet aggregation.

Moreover, SIRT1 inserts anti-inflammatory properties primarily by reducing oxidative stress (Bettioli et al. 2023). Studies have suggested several hypothetical mechanisms through which RSV may influence SIRT1 activation and impact the incidence of DVT and PE (Lou et al. 2017; Lou et al. 2021; Yao et al. 2019). A study observed that a higher degree of DVT is linked to more significant endothelium senescence and lower anti-aging gene SIRT expression. *In vivo* experiments revealed that over-expression of SIRT1 can prevent endothelial senescence and reduce the incidence of DVT. Also, the study found that its expression is low in the endothelium of severe thrombosis. Overexpressing lncRNA SIRT1-AS upregulated SIRT1 reduced the expression of senescence and DVT-related biomarkers in human vascular endothelial cells (HUVECs) (Lou et al. 2019). Recent studies suggest that the endothelial SIRT1 enzyme is vital in mitigating the harmful effects of hypoxia-induced endothelial dysfunction and thrombotic inflammation in DVT. This beneficial effect is achieved through the deacetylation of NF- κ B, a protein that plays a significant role in inflammatory processes. Essentially, the presence of endothelial SIRT1 helps to reduce the activity of NF- κ B, which in turn helps to alleviate the negative impacts of hypoxia-induced endothelial dysfunction and thrombotic inflammation in DVT (Tang et al. 2023).

RSV is also effective in mitigating intestinal ischemia-reperfusion injury by increasing SIRT3 expression and decreasing ferroptosis. Via activating the SIRT3/FoxO3a pathway, RSV enhances the SOD and CAT levels, minimizes ROS and LPO production, compensates for the GSH/GPX4 pathway, and inhibits ferroptosis. This promising research suggests that RSV has the potential to be a valuable tool in reducing intestinal ischemia-reperfusion injury (Wang et al. 2023). After being exposed to thrombin, the

levels of MCP-1, VCAM-1, ICAM-1, cleaved caspase 3, cleaved caspase 9, and Bax protein are increased (Liu et al. 2022). On the contrary, RSV caused a rise in the quantities of SIRT1 protein, which is recognized for its ability to protect against inflammation. Moreover, RSV caused an increase in the levels of messenger ribonucleic acid (mRNA) that encodes SIRT1 (Yao et al. 2019). The regulation of p53 activity is of great interest in the context of DVT, a potentially life-threatening condition characterized by the formation of blood clots in the deep veins of the body.

Intriguingly, recent studies have demonstrated that acetylated p53 levels are elevated in DVT models, suggesting a potential role for this modification in the pathogenesis of the disease. However, treatment with RSV, a natural polyphenolic compound known to activate SIRT1, significantly decreases acetylated p53 levels in DVT models. These findings suggest that SIRT1-mediated deacetylation of p53 may represent a potential therapeutic target for DVT treatment (Lou et al. 2021). One key factor that regulates platelet activity is cyclic AMP (cAMP). This molecule plays an important role in preventing platelet aggregation. A recent study by Park and colleagues found that RSV can directly inhibit cAMP-dependent phosphodiesterases. This inhibition sets off a series of events that ultimately affect two important metabolic regulators, AMPK and SIRT1 (Park et al. 2012). Various studies indicated that RSV attenuated P-selectin, PSGL-1, and vWF protein expression by H₂O₂ increase p53 and acetylated p53 and PAFR expression on platelets via SIRT1 signaling (Kim et al. 2016; Lou et al. 2017; Lou et al. 2021).

In general, the efficacy and mechanisms of RSV in the treatment of VTE are summarized in Figure 2.

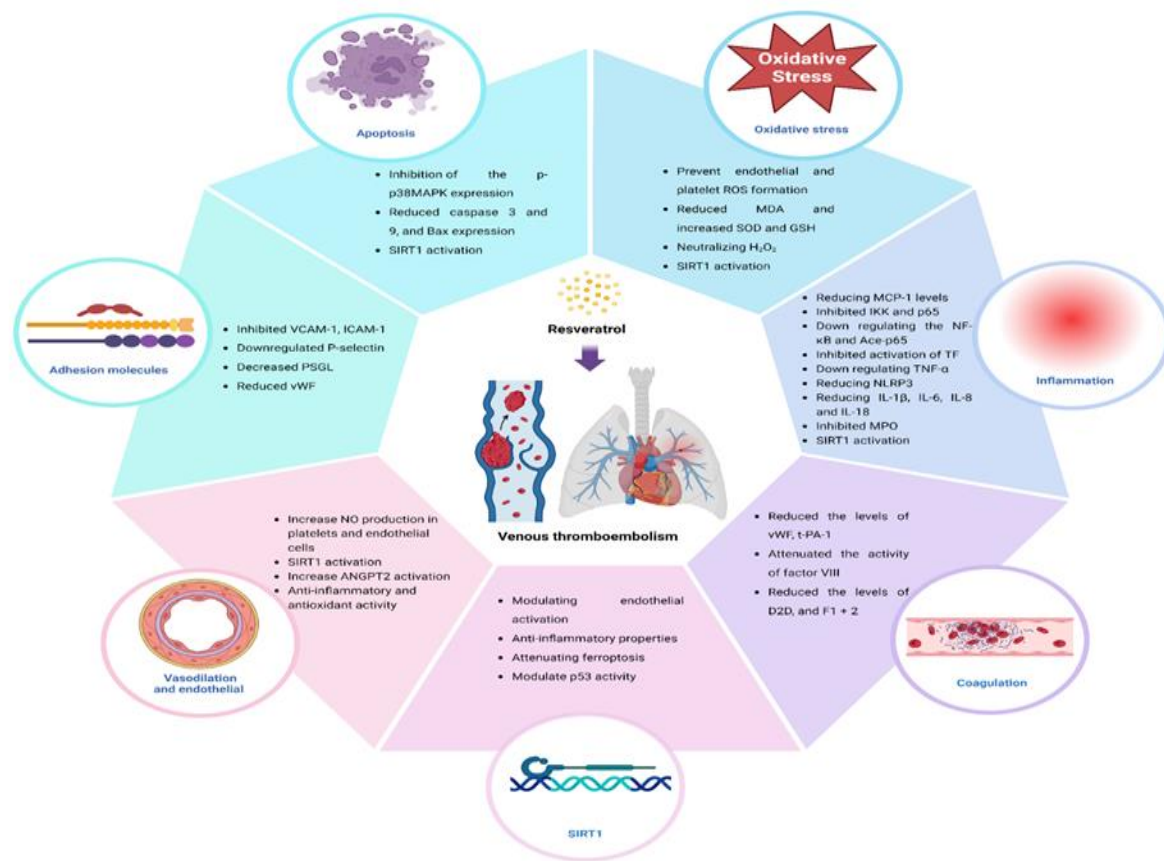


Figure 2. Main mechanistic effects of RSV against VTE (Created in: <https://www.biorender.com/>)

Most studies have preclinical designs and involve animal models or *in vitro* experiments. More well-designed controlled clinical trials are needed, which is one of the limitations of translating the findings to clinical practice. For the clinical use of RSV in the treatment of VTE, its long-term use and different doses should be investigated, and its drug interactions with other drugs and its side effects should be investigated more deeply.

Moreover, the included studies vary significantly in design, methodology, and patient populations. Heterogeneity across studies can make it challenging to draw consistent conclusions and may limit the generalizability of findings. There needs to be standardized dosages and treatment

durations across studies. Variability in the administered doses of RSV and the duration of interventions makes it challenging to establish optimal therapeutic regimens.

In vivo and *in vitro* studies revealed that RSV has promising effects on VTE through antioxidant, anti-inflammatory, anti-apoptosis, anticoagulation, and antiplatelet activity and inhibits adhesion molecules and vasodilation and endothelial protection properties. RSV has significant potential as a therapeutic agent for VTE prevention and treatment. However, further clinical investigations are necessary to confirm its effectiveness, establish standardized dosages, and ensure its safe integration into clinical practice.

Acknowledgment

None

Conflicts of interest

The authors declare there are no conflicts of interest

References

- Affara M, Dunmore B, Savoie C, et al. (2007) Understanding endothelial cell apoptosis: what can the transcriptome, glycome and proteome reveal? Philosophical transactions of the Royal Society of London Series B, Biological sciences 362(1484):1469-87 doi:10.1098/rstb.2007.2129
- Agno W, Donadini M (2018) Breadth of complications of long-term oral anticoagulant care. Hematology American Society of Hematology Education Program 2018(1):432-438 doi:10.1182/asheducation-2018.1.432
- Ahmad A, Dempsey SK, Daneva Z, et al. (2018) Role of Nitric Oxide in the Cardiovascular and Renal Systems. International journal of molecular sciences 19(9) doi:10.3390/ijms19092605
- Amini Chermahini F, Raeisi E, Aazami MH, Mirzaei A, Heidarian E, Lemoigne Y (2020) Does Bromelain-Cisplatin Combination Afford In-Vitro Synergistic Anticancer Effects on Human Prostatic Carcinoma Cell Line, PC3? Galen medical journal 9:e1749 doi:10.31661/gmj.v9i0.1749
- Banu KF, Ramya N, Reddy KS, Rekha R (2022) ANTI-THROMBOTIC AND ANTI-PLATELET ACTIVITY OF SOME ANTI-OXIDANTS. NeuroQuantology 20(11):7211
- Behraves S, Hoang P, Nanda A, et al. (2017) Pathogenesis of Thromboembolism and Endovascular Management. Thrombosis 2017:3039713 doi:10.1155/2017/3039713
- Berman AY, Motechin RA, Wiesenfeld MY, Holz MK (2017) The therapeutic potential of resveratrol: a review of clinical trials. NPJ precision oncology 1 doi:10.1038/s41698-017-0038-6
- Bettiol A, Galora S, Argento FR, et al. (2022) Erythrocyte oxidative stress and thrombosis. Expert reviews in molecular medicine 24:e31 doi:10.1017/erm.2022.25
- Bettiol A, Urban ML, Emmi G, et al. (2023) SIRT1 and thrombosis. Frontiers in molecular biosciences 10:1325002 doi:10.3389/fmolb.2023.1325002
- Bohara RA, Tabassum N, Singh MP, Gigli G, Ragusa A, Leporatti S (2022) Recent Overview of Resveratrol's Beneficial Effects and Its Nano-Delivery Systems. Molecules (Basel, Switzerland) 27(16) doi:10.3390/molecules27165154
- Braekkan SK, Grosse SD, Okoroh EM, et al. (2016) Venous thromboembolism and subsequent permanent work-related disability. Journal of thrombosis and haemostasis : JTH 14(10):1978-1987 doi:10.1111/jth.13411
- Branchford BR, Carpenter SL (2018) The Role of Inflammation in Venous Thromboembolism. Frontiers in pediatrics 6:142 doi:10.3389/fped.2018.00142
- Bui MH, Le QC, Duong DH, et al. (2020) Economic burden of venous thromboembolism in surgical patients: A propensity score analysis from the national claims database in Vietnam. PloS one 15(4):e0231411 doi:10.1371/journal.pone.0231411
- Caillon A, Trimaille A, Favre J, Jesel L, Morel O, Kauffenstein G (2022) Role of neutrophils, platelets, and extracellular vesicles and their interactions in COVID-19-associated thrombopathy. Journal of thrombosis and haemostasis : JTH 20(1):17-31 doi:10.1111/jth.15566
- Chen Y, Wang J, Liu C, et al. (2020) IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19. Molecular medicine

- (Cambridge, Mass) 26(1):97
doi:10.1186/s10020-020-00230-x
- Chun C, Yang W, Xueding C, et al. (2012) Resveratrol downregulates acute pulmonary thromboembolism-induced pulmonary artery hypertension via p38 mitogen-activated protein kinase and monocyte chemoattractant protein-1 signaling in rats. *Life sciences* 90(19-20):721-7
doi:10.1016/j.lfs.2012.03.008
- Cushnie B, Jaruchotikamol A, Laihakhot J, Chotson A (2024) In vitro antiglycation and antioxidant properties of ethanolic extracts of *Ficus botryocarpa* and *Ficus racemosa* fruits. *J Herbmед Pharmacol* 13(3):472-481
doi:10.34172/jhp.2024.51498
- D'Oria R, Schipani R, Leonardini A, et al. (2020) The Role of Oxidative Stress in Cardiac Disease: From Physiological Response to Injury Factor. *Oxidative medicine and cellular longevity* 2020:5732956
doi:10.1155/2020/5732956
- Drożdż D, Drożdż M, Wójcik M (2023) Endothelial dysfunction as a factor leading to arterial hypertension. *Pediatric nephrology (Berlin, Germany)* 38(9):2973-2985
doi:10.1007/s00467-022-05802-z
- Dutra LA, Guanaes JFO, Johann N, et al. (2017) Synthesis, antiplatelet and antithrombotic activities of resveratrol derivatives with NO-donor properties. *Bioorganic & medicinal chemistry letters* 27(11):2450-2453
doi:10.1016/j.bmcl.2017.04.007
- Ekor M (2014) The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 4:177
doi:10.3389/fphar.2013.00177
- El-Sayed OM, Dewyer NA, Luke CE, et al. (2016) Intact Toll-like receptor 9 signaling in neutrophils modulates normal thrombogenesis in mice. *Journal of vascular surgery* 64(5):1450-1458.e1
doi:10.1016/j.jvs.2015.08.070
- Fei J, Qin X, Ma H, et al. (2022) Resveratrol Ameliorates Deep Vein Thrombosis-Induced Inflammatory Response Through Inhibiting HIF-1 α /NLRP3 Pathway. *Inflammation* 45(6):2268-2279
doi:10.1007/s10753-022-01689-y
- Franchini M (2006) Hemostasis and aging. *Critical reviews in oncology/hematology* 60(2):144-51
doi:10.1016/j.critrevonc.2006.06.004
- Fukuhara S, Tsujimura A, Okuda H, et al. (2011) Vardenafil and resveratrol synergistically enhance the nitric oxide/cyclic guanosine monophosphate pathway in corpus cavernosal smooth muscle cells and its therapeutic potential for erectile dysfunction in the streptozotocin-induced diabetic rat: preliminary findings. *The journal of sexual medicine* 8(4):1061-71
doi:10.1111/j.1743-6109.2010.02193.x
- Gal R, Deres L, Toth K, Halmosi R, Habon T (2021) The Effect of Resveratrol on the Cardiovascular System from Molecular Mechanisms to Clinical Results. *International journal of molecular sciences* 22(18)
doi:10.3390/ijms221810152
- Gaur R, Chauhan A, Kanta C (2024) A critical review of antioxidant potential and pharmacological applications of important *Ficus* species. *J Herbmед Pharmacol* 13(4):537-549
doi:10.34172/jhp.2024.52557
- Genovesi S, Giussani M, Orlando A, Lieti G, Viazzi F, Parati G (2022) Relationship between endothelin and nitric oxide pathways in the onset and maintenance of hypertension in children and adolescents. *Pediatric nephrology (Berlin, Germany)* 37(3):537-545
doi:10.1007/s00467-021-05144-2
- Glorigijević N, Stanić-Vučinić D, Radomirović M, et al. (2021) Role of Resveratrol in Prevention and Control of Cardiovascular

- Disorders and Cardiovascular Complications Related to COVID-19 Disease: Mode of Action and Approaches Explored to Increase Its Bioavailability. *Molecules* (Basel, Switzerland) 26(10) doi:10.3390/molecules26102834
- Gonzalez-Quesada C, Frangogiannis NG (2009) Monocyte chemoattractant protein-1/CCL2 as a biomarker in acute coronary syndromes. *Current atherosclerosis reports* 11(2):131-8 doi:10.1007/s11883-009-0021-y
- Gordish KL, Beierwaltes WH (2014) Resveratrol induces acute endothelium-dependent renal vasodilation mediated through nitric oxide and reactive oxygen species scavenging. *American journal of physiology Renal physiology* 306(5):F542-50 doi:10.1152/ajprenal.00437.2013
- Granger V, Faille D, Marani V, et al. (2017) Human blood monocytes are able to form extracellular traps. *Journal of leukocyte biology* 102(3):775-781 doi:10.1189/jlb.3MA0916-411R
- Gross PL, Aird WC (2000) The endothelium and thrombosis. *Seminars in thrombosis and hemostasis* 26(5):463-78 doi:10.1055/s-2000-13202
- Gu T, Wang N, Wu T, Ge Q, Chen L (2021) Antioxidative Stress Mechanisms behind Resveratrol: A Multidimensional Analysis. *Journal of Food Quality* 2021:5571733 doi:10.1155/2021/5571733
- Guo X, Yuan S, Liu Z, Fang Q (2014) Oxidation- and CaMKII-mediated sarcoplasmic reticulum Ca(2+) leak triggers atrial fibrillation in aging. *Journal of cardiovascular electrophysiology* 25(6):645-52 doi:10.1111/jce.12395
- Han Y, Bai X, Wang X (2022) Exosomal myeloperoxidase as a biomarker of deep venous thrombosis. *Annals of translational medicine* 10(1):9 doi:10.21037/atm-21-5583
- Hobohm L, Kölmel S, Niemann C, et al. (2021) Role of angiopoietin-2 in venous thrombus resolution and chronic thromboembolic disease. *The European respiratory journal* 58(6) doi:10.1183/13993003.04196-2020
- Hong J, Ahn SY, Lee YJ, et al. (2021) Updated recommendations for the treatment of venous thromboembolism. *Blood research* 56(1):6-16 doi:10.5045/br.2021.2020083
- Hsia C-W, Huang W-C, Yang C-H, et al. (2021) Comparison of the Potency of Pterostilbene with NF-κB Inhibitors in Platelet Activation: Mutual Activation by Akt-NF-κB Signaling in Human Platelets. *Applied Sciences* 11(13):6149
- Huang SL, Xin HY, Wang XY, et al. (2023) Recent Advances on the Molecular Mechanism and Clinical Trials of Venous Thromboembolism. *Journal of inflammation research* 16:6167-6178 doi:10.2147/jir.s439205
- Huang TY, Yu CP, Hsieh YW, Lin SP, Hou YC (2020) Resveratrol stereoselectively affected (±)warfarin pharmacokinetics and enhanced the anticoagulation effect. *Scientific reports* 10(1):15910 doi:10.1038/s41598-020-72694-0
- Huang WC, Liu JC, Hsia CW, et al. (2021) Pterostilbene, a Dimethylether Analogue of Resveratrol, Possesses High Potency in the Prevention of Platelet Activation in Humans and the Reduction of Vascular Thrombosis in Mice. *Journal of agricultural and food chemistry* 69(16):4697-4707 doi:10.1021/acs.jafc.1c00367
- Humphries J, McGuinness CL, Smith A, Waltham M, Poston R, Burnand KG (1999) Monocyte chemotactic protein-1 (MCP-1) accelerates the organization and resolution of venous thrombi. *Journal of vascular surgery* 30(5):894-9 doi:10.1016/s0741-5214(99)70014-5
- Izzo C, Annunziata M, Melara G, et al. (2021a) The Role of Resveratrol in Liver Disease: A Comprehensive Review from In Vitro to

- Clinical Trials. *Nutrients* 13(3) doi:10.3390/nu13030933
- Izzo C, Vitillo P, Di Pietro P, et al. (2021b) The Role of Oxidative Stress in Cardiovascular Aging and Cardiovascular Diseases. *Life* (Basel, Switzerland) 11(1) doi:10.3390/11010060
- Jivad N, Heidari-Soureshjani S, Bagheri H, Sherwin CM, Rostamian S (2024) Anti-seizure Effects and Mechanisms of Berberine: A Systematic Review. *Current pharmaceutical biotechnology* doi:10.2174/0113892010283237240107121 749
- Khaledifar A, Khosravi Farsani MR, Raeisi E (2023) Berberine efficacy against Doxorubicin-induced cardiotoxicity: A systematic review. *J Herbmed Pharmacol* 12(2):187-193 doi:10.34172/jhp.2023.19
- Kim YH, Bae JU, Kim IS, Chang CL, Oh SO, Kim CD (2016) SIRT1 prevents pulmonary thrombus formation induced by arachidonic acid via downregulation of PAF receptor expression in platelets. *Platelets* 27(8):735-742 doi:10.1080/09537104.2016.1190005
- Kirimlioglu V, Sozen H, Turkoglu S, Haberal M (2008) Protective effect of resveratrol, a red wine constituent polyphenol, on rats subjected to portal vein thrombosis. *Transplantation proceedings* 40(1):290-2 doi:10.1016/j.transproceed.2007.11.051
- Konyalioglu S, Armagan G, Yalcin A, Atalayin C, Dagci T (2013) Effects of resveratrol on hydrogen peroxide-induced oxidative stress in embryonic neural stem cells. *Neural regeneration research* 8(6):485-95 doi:10.3969/j.issn.1673-5374.2013.06.001
- Labarrere CA, Dabiri AE, Kassab GS (2020) Thrombogenic and Inflammatory Reactions to Biomaterials in Medical Devices. *Frontiers in bioengineering and biotechnology* 8:123 doi:10.3389/fbioe.2020.00123
- Landau N, Shoenfeld Y, Negru L, Segal G (2022) Exploring the pathways of inflammation and coagulopathy in COVID-19: A narrative tour into a viral rabbit hole. *International reviews of immunology* 41(4):414-422 doi:10.1080/08830185.2021.1993211
- Lebreton F, Berishvili E, Parnaud G, et al. (2018) NLRP3 inflammasome is expressed and regulated in human islets. *Cell death & disease* 9(7):726 doi:10.1038/s41419-018-0764-x
- Ley K, Laudanna C, Cybulsky MI, Nourshargh S (2007) Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nature reviews Immunology* 7(9):678-89 doi:10.1038/nri2156
- Li H, Xia N, Hasselwander S, Daiber A (2019) Resveratrol and Vascular Function. *International journal of molecular sciences* 20(9) doi:10.3390/ijms20092155
- Lin JW, Yang LH, Ren ZC, et al. (2019) Resveratrol downregulates TNF- α -induced monocyte chemoattractant protein-1 in primary rat pulmonary artery endothelial cells by P38 mitogen-activated protein kinase signaling. *Drug design, development and therapy* 13:1843-1853 doi:10.2147/dddt.s184785
- Liu X, Zhou H, Hu Z (2022) Resveratrol attenuates chronic pulmonary embolism-related endothelial cell injury by modulating oxidative stress, inflammation, and autophagy. *Clinics (Sao Paulo, Brazil)* 77:100083 doi:10.1016/j.clinsp.2022.100083
- Longstaff C, Kolev K (2015) Basic mechanisms and regulation of fibrinolysis. *Journal of thrombosis and haemostasis : JTH* 13 Suppl 1:S98-105 doi:10.1111/jth.12935
- Lou Z, Du K, Wang T, Zhao X, Li X, Wang B (2017) Resveratrol suppresses P-selectin, PSGL-1, and VWF through SIRT1 signaling pathway. *Acta biochimica et biophysica Sinica* 49(9):848-850 doi:10.1093/abbs/gmx077

- Lou Z, Li X, Li X, et al. (2019) LncRNA Sirt1-AS Up-Regulates Sirt1 to Improve the Aging-Related Deep Venous Thrombosis.
- Lou Z, Li X, Zhao X, Du K, Li X, Wang B (2018a) Resveratrol attenuates hydrogen peroxide-induced apoptosis, reactive oxygen species generation, and PSGL-1 and VWF activation in human umbilical vein endothelial cells, potentially via MAPK signalling pathways. *Molecular medicine reports* 17(2):2479-2487
- Lou Z, Li X, Zhao X, Du K, Li X, Wang B (2018b) Resveratrol attenuates hydrogen peroxide-induced apoptosis, reactive oxygen species generation, and PSGL-1 and VWF activation in human umbilical vein endothelial cells, potentially via MAPK signalling pathways. *Molecular medicine reports* 17(2):2479-2487 doi:10.3892/mmr.2017.8124
- Lou Z, Zhu J, Li X, et al. (2021) LncRNA Sirt1-AS upregulates Sirt1 to attenuate aging related deep venous thrombosis. *Aging* 13(5):6918-6935 doi:10.18632/aging.202550
- Lu Z, Wang S, Zhu X, et al. (2019) Resveratrol Induces Endothelial Progenitor Cells Angiogenesis via MiR-542-3p by Targeting Angiopoietin-2 and Involves in Recanalization of Venous Thrombosis. *Medical science monitor : international medical journal of experimental and clinical research* 25:7675-7683 doi:10.12659/msm.917013
- Lyhne MD, Kline JA, Nielsen-Kudsk JE, Andersen A (2020) Pulmonary vasodilation in acute pulmonary embolism - a systematic review. *Pulmonary circulation* 10(1):2045894019899775 doi:10.1177/2045894019899775
- Mallat Z, Tedgui A (2000) Apoptosis in the vasculature: mechanisms and functional importance. *British journal of pharmacology* 130(5):947-62 doi:10.1038/sj.bjp.0703407
- Marcos-Jubilar M, Lecumberri R, Páramo JA (2023) Immunothrombosis: Molecular Aspects and New Therapeutic Perspectives. *Journal of clinical medicine* 12(4) doi:10.3390/jcm12041399
- Martinez C, Katholing A, Wallenhorst C, Cohen AT (2020) Prediction of significant bleeding during vitamin K antagonist treatment for venous thromboembolism in outpatients. *British journal of haematology* 189(3):524-533 doi:10.1111/bjh.16383
- Masselli E, Pozzi G, Vaccarezza M, et al. (2020) ROS in Platelet Biology: Functional Aspects and Methodological Insights. *International journal of molecular sciences* 21(14) doi:10.3390/ijms21144866
- McCalley AE, Kaja S, Payne AJ, Koulen P (2014) Resveratrol and calcium signaling: molecular mechanisms and clinical relevance. *Molecules (Basel, Switzerland)* 19(6):7327-40 doi:10.3390/molecules19067327
- McCreary MR, Schnell PM, Rhoda DA (2022) Randomized double-blind placebo-controlled proof-of-concept trial of resveratrol for outpatient treatment of mild coronavirus disease (COVID-19). *Scientific reports* 12(1):10978 doi:10.1038/s41598-022-13920-9
- Molla MD, Akalu Y, Geto Z, Dagne B, Ayelign B, Shibabaw T (2020) Role of Caspase-1 in the Pathogenesis of Inflammatory-Associated Chronic Noncommunicable Diseases. *Journal of inflammation research* 13:749-764 doi:10.2147/jir.s277457
- Moris D, Spartalis M, Tzatzaki E, et al. (2017) The role of reactive oxygen species in myocardial redox signaling and regulation. *Annals of translational medicine* 5(16):324 doi:10.21037/atm.2017.06.17
- Moshfegh F, Baharara J, Namvar F, Zafar-Balanezhad S, Amini E, Jafarzadeh L (2016) Effects of date palm pollen on fertility and development of reproductive system in

- female Balb/C mice. *J Herbmmed Pharmacol* 5(1):23-28
- Mukherjee AK, Chattopadhyay DJ (2022) Potential clinical applications of phytopharmaceuticals for the in-patient management of coagulopathies in COVID-19. *Phytotherapy research : PTR* 36(5):1884-1913 doi:10.1002/ptr.7408
- Müller I, Klocke A, Alex M, et al. (2003) Intravascular tissue factor initiates coagulation via circulating microvesicles and platelets. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 17(3):476-8 doi:10.1096/fj.02-0574fje
- Nan W, He Y, Wang S, Zhang Y (2023) Molecular mechanism of VE-cadherin in regulating endothelial cell behaviour during angiogenesis. *Frontiers in physiology* 14:1234104 doi:10.3389/fphys.2023.1234104
- Oak MH, Auger C, Belcastro E, Park SH, Lee HH, Schini-Kerth VB (2018) Potential mechanisms underlying cardiovascular protection by polyphenols: Role of the endothelium. *Free radical biology & medicine* 122:161-170 doi:10.1016/j.freeradbiomed.2018.03.018
- Palareti G, Antonucci E, Legnani C, et al. (2020) Bleeding and thrombotic complications during treatment with direct oral anticoagulants or vitamin K antagonists in venous thromboembolic patients included in the prospective, observational START2-register. *BMJ open* 10(11):e040449 doi:10.1136/bmjopen-2020-040449
- Palta S, Saroa R, Palta A (2014) Overview of the coagulation system. *Indian journal of anaesthesia* 58(5):515-23 doi:10.4103/0019-5049.144643
- Pan Z, Dong H, Huang N, Fang J (2022) Oxidative stress and inflammation regulation of sirtuins: New insights into common oral diseases. *Frontiers in physiology* 13:953078 doi:10.3389/fphys.2022.953078
- Park SJ, Ahmad F, Philp A, et al. (2012) Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell* 148(3):421-33 doi:10.1016/j.cell.2012.01.017
- Pendurthi UR, Williams JT, Rao LV (1999) Resveratrol, a polyphenolic compound found in wine, inhibits tissue factor expression in vascular cells : A possible mechanism for the cardiovascular benefits associated with moderate consumption of wine. *Arteriosclerosis, thrombosis, and vascular biology* 19(2):419-26 doi:10.1161/01.atv.19.2.419
- Periayah MH, Halim AS, Mat Saad AZ (2017) Mechanism Action of Platelets and Crucial Blood Coagulation Pathways in Hemostasis. *International journal of hematology-oncology and stem cell research* 11(4):319-327
- Pham-Huy LA, He H, Pham-Huy C (2008) Free radicals, antioxidants in disease and health. *International journal of biomedical science : IJBS* 4(2):89-96
- Pilard M, Ollivier EL, Gourdou-Latyszenok V, Couturaud F, Lemarié CA (2022) Endothelial Cell Phenotype, a Major Determinant of Venous Thrombo-Inflammation. *Frontiers in cardiovascular medicine* 9:864735 doi:10.3389/fcvm.2022.864735
- Pizzino G, Irrera N, Cucinotta M, et al. (2017) Oxidative Stress: Harms and Benefits for Human Health. *Oxidative medicine and cellular longevity* 2017:8416763 doi:10.1155/2017/8416763
- Planinc M, Jovanović IN, Rašić D, Peraica M, Sutlić Ž (2022) Resveratrol as antioxidant in cardiac surgery: is there potential for clinical application? *Arhiv za higijenu rada i toksikologiju* 73(4):256-259 doi:10.2478/aiht-2022-73-3643

- Poredos P, Jezovnik MK (2007) The role of inflammation in venous thromboembolism and the link between arterial and venous thrombosis. *International angiology : a journal of the International Union of Angiology* 26(4):306-11
- Previtali E, Bucciarelli P, Passamonti SM, Martinelli I (2011) Risk factors for venous and arterial thrombosis. *Blood transfusion = Trasfusione del sangue* 9(2):120-38 doi:10.2450/2010.0066-10
- Protić D, Beleslin-Čokić B, Novaković R, et al. (2013) Effect of wine polyphenol resveratrol on the contractions elicited electrically or by norepinephrine in the rat portal vein. *Phytotherapy research : PTR* 27(11):1685-93 doi:10.1002/ptr.4907
- Ramírez-Garza SL, Laveriano-Santos EP, Marhuenda-Muñoz M, et al. (2018) Health Effects of Resveratrol: Results from Human Intervention Trials. *Nutrients* 10(12) doi:10.3390/nu10121892
- Roy A, Roy M, Gacem A, et al. (2022) Role of bioactive compounds in the treatment of hepatitis: A review. *Front Pharmacol* 13:1051751 doi:10.3389/fphar.2022.1051751
- Shahidi M, Parhizkary F, Sharifi R, Ghotaslou A, Barati M (2020) Effects of resveratrol on coagulative, fibrinolytic, and inflammatory marker expression and secretion by endothelial cells (human umbilical vein endothelial cells). *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis* 31(3):207-212 doi:10.1097/mbc.0000000000000900
- Siti HN, Kamisah Y, Kamsiah J (2015) The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vascular pharmacology* 71:40-56 doi:10.1016/j.vph.2015.03.005
- Stark K, Massberg S (2021) Interplay between inflammation and thrombosis in cardiovascular pathology. *Nature reviews Cardiology* 18(9):666-682 doi:10.1038/s41569-021-00552-1
- Stone J, Hangge P, Albadawi H, et al. (2017) Deep vein thrombosis: pathogenesis, diagnosis, and medical management. *Cardiovascular diagnosis and therapy* 7(Suppl 3):S276-s284 doi:10.21037/cdt.2017.09.01
- Talib WH, Alsayed AR, Farhan F, Al Kury LT (2020) Resveratrol and Tumor Microenvironment: Mechanistic Basis and Therapeutic Targets. *Molecules (Basel, Switzerland)* 25(18) doi:10.3390/molecules25184282
- Tang P, Wang Y, Yang X, et al. (2023) Protective Role of Endothelial SIRT1 in Deep Vein Thrombosis and Hypoxia-induced Endothelial Dysfunction Mediated by NF-κB Deacetylation. *Inflammation* 46(5):1887-1900 doi:10.1007/s10753-023-01848-9
- Tromba L, Perla FM, Carbotta G, Chiesa C, Pacifico L (2019) Effect of Alpha-Lipoic Acid Supplementation on Endothelial Function and Cardiovascular Risk Factors in Overweight/Obese Youths: A Double-Blind, Placebo-Controlled Randomized Trial. *Nutrients* 11(2) doi:10.3390/nu11020375
- van Hinsbergh VW (2012) Endothelium--role in regulation of coagulation and inflammation. *Seminars in immunopathology* 34(1):93-106 doi:10.1007/s00281-011-0285-5
- Vogel S, Thein SL (2018) Platelets at the crossroads of thrombosis, inflammation and haemolysis. *British journal of haematology* 180(5):761-767 doi:10.1111/bjh.15117
- Vrotniakaite-Bajerciene K, Rütsche S, Calzavarini S, et al. (2023) Thrombin Generation Is Associated with Venous Thromboembolism Recurrence, but Not with Major Bleeding and Death in the Elderly: A Prospective Multicenter Cohort Study. *Journal of clinical medicine* 12(18) doi:10.3390/jcm12186050

- Wang Q, Yu Q, Wu M (2022) Antioxidant and neuroprotective actions of resveratrol in cerebrovascular diseases. *Frontiers in pharmacology* 13:948889 doi:10.3389/fphar.2022.948889
- Wang Q, Zennadi R (2020) Oxidative Stress and Thrombosis during Aging: The Roles of Oxidative Stress in RBCs in Venous Thrombosis. *International journal of molecular sciences* 21(12) doi:10.3390/ijms21124259
- Wang X, Shen T, Lian J, et al. (2023) Resveratrol reduces ROS-induced ferroptosis by activating SIRT3 and compensating the GSH/GPX4 pathway. *Molecular medicine (Cambridge, Mass)* 29(1):137 doi:10.1186/s10020-023-00730-6
- Wong DJ, Park DD, Park SS, et al. (2021) A PSGL-1 glycomimetic reduces thrombus burden without affecting hemostasis. *Blood* 138(13):1182-1193 doi:10.1182/blood.2020009428
- WU W, Chen X (2016) Effect of Resveratrol on the Expression of MCP-1 and BNP in Myocardial Cells of Rats with Acute Pulmonary Embolism. *Acta Medicinæ Universitatis Scientiæ et Technologiæ Huazhong*:311-314
- Xu M, Xue W, Ma Z, Bai J, Wu S (2016) Resveratrol Reduces the Incidence of Portal Vein System Thrombosis after Splenectomy in a Rat Fibrosis Model. *Oxidative medicine and cellular longevity* 2016:7453849 doi:10.1155/2016/7453849
- Yang K, Li W, Duan W, et al. (2019) Resveratrol attenuates pulmonary embolism associated cardiac injury by suppressing activation of the inflammasome via the MALAT1-miR-22-3p signaling pathway. *International journal of molecular medicine* 44(6):2311-2320 doi:10.3892/ijmm.2019.4358
- Yao M, Ma J, Wu D, et al. (2023) Neutrophil extracellular traps mediate deep vein thrombosis: from mechanism to therapy. *Frontiers in immunology* 14:1198952 doi:10.3389/fimmu.2023.1198952
- Yao X, Chen W, Liu J, et al. (2019) Deep Vein Thrombosis is Modulated by Inflammation Regulated via Sirtuin 1/NF-κB Signalling Pathway in a Rat Model. *Thrombosis and haemostasis* 119(3):421-430 doi:10.1055/s-0038-1676987
- Zhan G, Wenhua G, Jie H, et al. (2018) Potential roles of circulating matrix metalloproteinase-28 (MMP-28) in patients with atrial fibrillation. *Life sciences* 204:15-19 doi:10.1016/j.lfs.2018.04.053
- Zhang Y, Du X, Li W, et al. (2018) Resveratrol Improves Endothelial Progenitor Cell Function through miR-138 by Targeting Focal Adhesion Kinase (FAK) and Promotes Thrombus Resolution In Vivo. *Medical science monitor : international medical journal of experimental and clinical research* 24:951-960 doi:10.12659/msm.906116
- Zhou Y, Tao W, Shen F, Du W, Xu Z, Liu Z (2021) The Emerging Role of Neutrophil Extracellular Traps in Arterial, Venous and Cancer-Associated Thrombosis. *Frontiers in cardiovascular medicine* 8:786387 doi:10.3389/fcvm.2021.786387
- Zhou Y, Xu Z, Liu Z (2022) Impact of Neutrophil Extracellular Traps on Thrombosis Formation: New Findings and Future Perspective. *Frontiers in cellular and infection microbiology* 12:910908 doi:10.3389/fcimb.2022.910908.

