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# Nano Drug Delivery System with Resveratrol as Promising Novel Adjuvant Therapy for Diabetic Non-Healing Wounds: A Literature Review

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## ABSTRACT

Diabetes mellitus (DM) is a metabolic disease characterized by increased blood sugar levels (hyperglycemia) and is associated with impaired function of β cells. The uncontrolled and prolonged hyperglycemia in DM can cause complications. One of the most common is diabetic non-healing wounds, the leading cause of disability in people with diabetes, therefore adjuvant therapy is needed. Compounds from natural ingredients are currently getting the spotlight in recent studies conducted to prove their effect on non-healing wounds, such as Resveratrol (RSV). This review aims to discuss the potential of RSV as a novel adjuvant therapy and its delivery system strategy in the case of diabetic non-healing wounds. We conducted an extensive search from three online scientific databases such as ScienceDirect, ResearchGate, and PubMed on February-March 2023. Keywords used are "resveratrol", "diabetic wound healing", and "diabetes mellitus". As a result, 86 studies were reviewed, and only 79 selected studies met all inclusion criteria. The formulation of RSV nanoparticles in oral drug delivery systems and topical administration has shown promise to overcome the limitations of RSV as adjuvant therapy in diabetic non-healing wounds. The best option that we found through this literature review is the nano-oral drug delivery system as it could minimize drug metabolism in the gastrointestinal tract, therefore the drug bioavailability and drug concentration on the target site could be maximized, even though the systemic side effects might occur.

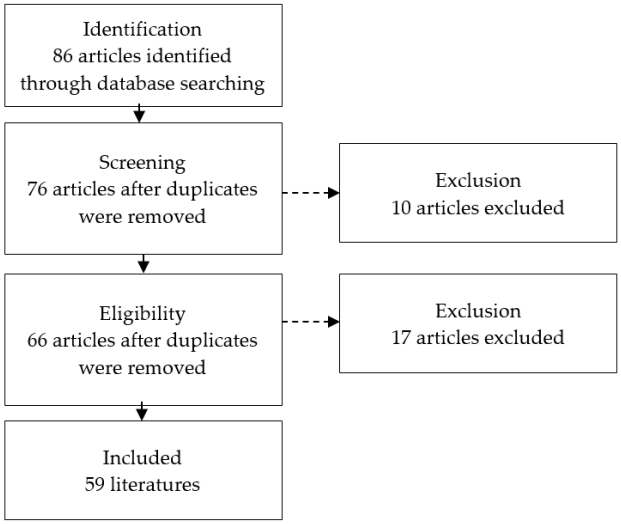
**Keywords**: Nano-resveratrol; Type 2 Diabetes Mellitus; Diabetic Non-Healing Wounds

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease denoted by increased blood sugar levels (hyperglycemia) and associated with impaired function of β cells[1,2]. There are several groupings of DM, but the primary classifications are type 1 diabetes mellitus (T1DM) due to defects in insulin secretion and type 2 diabetes mellitus (T2DM) due to insulin resistance[3]. Diabetes is a health problem in almost every country, with a trend that has not shown a decline yearly.

According to data from the International Diabetic Federation (IDF), the prevalence of T2DM in the age range 20-79 years at any point in time in 2017 was 425 million. This number increased to 536.6 million in 2021 and is projected to reach 783.2 million in 2045[4,5]. The condition of uncontrolled and prolonged hyperglycemia in DM can cause complications. One of the most common is a wound that is difficult to heal or cannot heal. Globally, this complication was found in 6.3% of people with diabetes in 2017, which is also increasing as the incidence of diabetes increases yearly[4]. Diabetic non-healing wounds can cause amputation, the leading cause of disability in people with diabetes. Oxidative stress plays a vital role due to increased reactive oxygen species (ROS), causing diabetic wounds to be more difficult to heal than normal wounds[6,7].

Management of diabetic wounds currently requires the standard wound toilet and debridement, administration of antibiotics, and glycemic control with DM drugs[8]. However, in some cases of more severe injuries, standard treatment alone is insufficient to close the wound and prevent amputation. For maximum outcome, adjuvant therapy is also being pursued, and its effectiveness has begun to be investigated in healing strategies with diabetic wound closure as the primary goal. Antioxidants and anti-inflammatory agents are known to be capable of detoxifying ROS so that in the pathogenesis




of diabetic wounds, they can help improve healing and wound healing time[7]. Compounds from natural ingredients are currently getting the spotlight in recent studies conducted to prove their effect on non-healing wounds[9]. Resveratrol (RSV) is one of them. It contains promising antioxidant and anti-inflammatory effects to help faster healing and improve wound healing outcomes by targeting nuclear-factor-E2-related factor-2 (Nrf2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and sirtuin 1 (SIRT-1), signaling pathway[10,11]. However, the potential of RSV is not supported by several limitations, primarily since RSV is metabolized rapidly. Hence, its concentration when it reaches the target organ is small, and its bioavailability is low. In addition, the administration of higher doses of RSV can cause adverse effects, which change the ability of RSV to become toxic. Thus, modifications in the form of RSV nanoformulation were developed to overcome these limitations. Nano formulation can help RSV penetrate mucous and epithelial membranes, increase oral bioavailability, and prolong particle circulation in the bloodstream[12,13]. Nano formulation technology can also provide controlled and targeted drug release effects. So, it can work synergistically with the effects of RSV. Based on that, we are interested in comprehensively discussing the potential of RSV as a novel adjuvant therapy and its delivery system strategy in the case of diabetic non-healing wounds.

## METHODS

Literature searching was done in February 2023 and ended in March 2023 in three online scientific databases there are Science Direct, ResearchGate, and PubMed. Keywords that are used in the literature search are “resveratrol”, “diabetic wound healing”, and “diabetes mellitus”. We use Boolean search: "Resveratrol" or "RSV" or "RES" and "nano formulation" or "nanoparticles" and "diabetic wound healing" and "diabetic non-healing wound" or "diabetic non-healing wound" and "diabetic wound" and "diabetes mellitus".

The inclusion criteria of this literature review were all of the references that discussed the delivery system of resveratrol and its impact on diabetic non-healing wounds adjuvant therapy, specifically with nano drug delivery system. Exclusion criteria were a literature that is older than 2012 unless no newer studies were found to argue regarding the content and studies that are not written in English, As a result, we found 59 out of 86 works of literature that match our keywords and criteria: 45 from PubMed, 2 from Science Direct, and 12 from ResearchGate. Data types of the literature are mostly qualitative type one.

## RESULT AND DISCUSSION

### Details of Selected Studies

The retrieved studies consisted of a varied number of primary and secondary sources such as in vivo or in vitro trials and article reviews. They were published from different kinds of sites. We also found a variety of years of publication within the study, with all studies conducted in the last 11 years (2012-2023). Variations of the study sample came from a wide range of ages and populations.

### Properties of Resveratrol

The bioactive compound extracted from Japanese knotweed, peanuts, grapes, and berries is resveratrol (3,5,4'-trihydroxystilbene), a non-polyphenolic compound in the form of stilbene derivatives[14,15]. RSV is a natural polyphenol and phytoalexin with numerous potential health benefits. The plants secrete RSV as their innate immune response towards pathogens, harmful environments, and other threats to the plants[16,17]. RSV has lipophilic properties and low molecular weight (228 Da) compared to other stilbene derivatives; thus, it can enter deeper layers better[18]. It has anti-inflammatory, immunomodulatory, antioxidant, and protective effects against various diseases, including cancer, cardiovascular, neurodegenerative, and diabetes[19,20]. In diabetic non-healing wounds, RSV can potentially benefit through its antioxidant and anti-inflammatory effects to help improve the healing response and shorten the healing duration.

*Antioxidant properties*

As an antioxidant, RSV can inhibit or slow down the occurrence of oxidative injury to cells. RSV has a structural component: the hydroxyl group (-OH) in its aromatic ring. This structure gives RSV the ability as an oxide-reducing agent and electron donor to neutralize excessive Reactive Oxygen Species (ROS)[21,22]. In addition, aside from directly eliminating free radicals, RSV has another mechanism of action in its role as an antioxidant. RSV can increase the number of endogenous antioxidants, such as glutathione peroxidase (GSH-Px), catalase (CAT), superoxide dismutase (SOD), etc[9,23]. This ability is because RSV can stimulate the transcription factor Nrf2 which is essential in regulating the synthesis of endogenous antioxidant enzymes [Figure 1]. RSV also has an indirect interaction with SIRT-1, an NAD+-dependent protein involved in the mechanism of cell self-repairing due to oxidative stress. Previous studies stated that RSV plays a role in inhibiting the action of the phosphodiesterase (PDE) enzyme so that cAMP is not degraded to AMP and AMPK activation occurs, which then increases NAD+ levels. An increase in the amount of NAD+ causes SIRT-1 activation[10,24]

*Anti-inflammatory properties*

The inflammatory response in the body occurs because it is triggered by an injury that occurs in healthy tissue due to infectious or non-infectious stimuli. Inflammation that occurs acutely contributes to the body's self-defense mechanism, which is essential in removing harmful stimuli and restoring homeostasis[25,26]. However, it becomes a problem in chronic inflammatory conditions due to uncontrolled inflammation. Based on previous in vivo and in vitro studies, dose-dependent RSV has been shown to have anti-inflammatory properties due to its ability to inhibit the synthesis and expression of pro-inflammatory molecules [interleukines-1β, -6, -8, tumor necrosis factor $\alpha$ (TNF- $\alpha$)][27–30]. This effect is due to the interaction of RSV with several molecular targets, such as MAPK, SIRT1, AP-1, and NF-κB signaling. RSV can inhibit the action of this molecule as a mediator of pro-inflammatory responses in chronic inflammation, for example, in diabetic wounds[31].

### Pathogenesis of Diabetic non-Healing Wounds

Many complications are attributable to DM and its chronic nature. As much as 25% of DM patients are at risk for developing diabetic non-healing foot ulcers or diabetic non-healing wounds[32]. The terminology for non-healing wounds is defined as wounds that fail to heal spontaneously within a period of 3

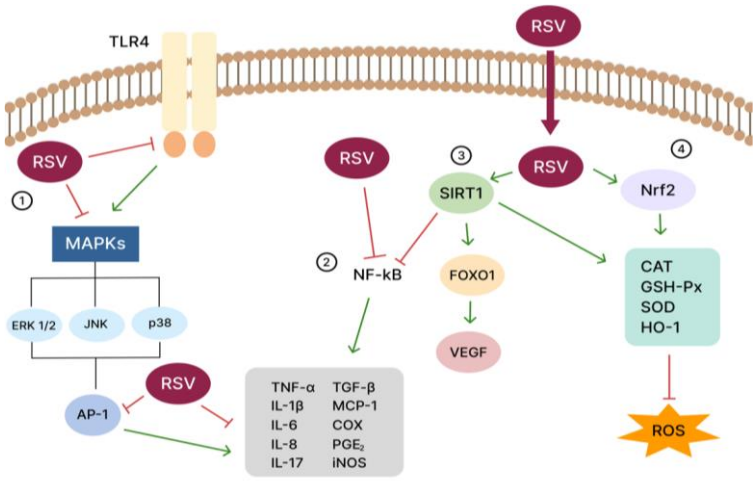



**Figure 1. Schematic diagram of RSV's antioxidant and anti-inflammatory activities, and their potential molecular target. (1) MAPK pathway, (2) NF-κB pathway, (3) SIRT1 pathway, involved in the anti-inflammatory mechanism of RSV. In addition, by increasing SIRT1 activity, RSV can increase angiogenesis to accelerate wound healing (4) Nrf2 pathway, involved in the antioxidant activity of RSV by increasing endogenous antioxidants.**

months[33]. Wound healing is a dynamic process that begins when tissue integrity is disrupted, consisting of 4 phases: hemostasis, inflammation, proliferative, and remodeling phase. High-quality wound healing requires corresponding integration between cell migration, cell proliferation, and extracellular matrix (ECM)[34]. Diabetes mellitus can interfere with the wound-healing process that is mentioned above. Defects in microcirculation, peripheral neuropathy, and peripheral arterial disease that can be seen in DM could impair the wound-healing process. Impaired diabetic wound healing is more common in areas that are affected by peripheral neuropathy. An altered immune response in DM patients causes lower resistance of diabetic wounds to infection as the peripheral nervous system regulates immune response via neuropeptide substances. Therefore, effective therapies for DM and diabetic foot ulcers as complications require therapies that could restore both the molecular and cellular processes[35].

Non-healing wounds are ulcers that fail to heal after 12 weeks. They started as acute wounds but when the healing process was disrupted, they became chronic diabetes wounds which are now called diabetic non-healing wounds. Hyperglycemia, chronic inflammation, micro-circulatory and macro-circulatory dysfunction, hypoxia, impaired neuropeptide signaling, neuropathy, and impaired angiogenesis that occur in DM pathophysiology influenced the wound healing process in diabetic wounds [Figure. 2][35]. Diabetes could also make the wound environment more prone to bacterial colonization leading to catastrophic infection. Infection could cause more extensive inflammation. Therefore, more cytokines are released and result in a non-healing diabetic wound[36]. Hyperglycemia can lead to the formation of advanced glycation end products (AGE) that can diminish the extracellular matrix solubility and prolong the inflammatory phase in diabetes[35].

Chronic inflammation is found in patients with DM. A prolonged inflammatory state in diabetes interferes with the wound-healing process after injury. In the beginning, tissue injury triggers an acute inflammatory response which is marked by neutrophils, macrophages, and mast cells recruitment to the injury site. Elevated amounts of pro-

**Table Ia. Properties of RSV**

| Authors, year | Aim of Study | Type of Study | RSV properties |
|---|---|---|---|
| Colica et al (2018) | To summarize about healing and preventive potential of resveratrol, it acts as a cardioprotective, neuroprotective, chemopreventive, and antioxidant agent. | Systematic review | Many pre-clinical studies provided promising shreds of evidence about different resveratrol benefits and its recognition of well-tolerated and safe natural active compounds. However, the outcomes of clinical studies are inconsistent and limited. Regarding the poor bioavailability of most of the commercially available resveratrol supplements, the application of improved oral dosage forms is necessary. |
| Meng et al (2021) | To examine the anti-inflammatory activity and the mechanism of RSV in modulating inflammatory response | Narrative review | Phytoalexin was demonstrated to modulate many cellular and molecular mediators of inflammation, but the molecular mechanisms of polyphenol are complex and involve multiple signal transduction pathways, and have not been fully elucidated. |
| Jhaveri et al (2018) | To enhance the physicochemical properties of rsv and exploit the passive and active targeting capabilities of liposomes to effectively treat glioblastoma (GBM) | Experimental study | The liposome surface that was modified with transferrin moieties (Tf-RES-L) developed in this project showed an enhanced in vitro activity, which translated into a favorable therapeutic response in vivo compared to the free drug and non-targeted RES-L (RSV that was loaded into PEGylated liposomes). |
| Okamoto, Yoshida, and Ishihara (2021) | To investigate the effect of resveratrol against C. albicans biofilm formation | Experimental study | RSV has the potential to serve as an anti-Candida treatment and preventive tool that functions by inhibiting existing or under-forming C. albicans biofilms. |
| Gambini et al (2015) | To clarify aspects like stability and pharmacokinetics of RSV metabolites to understand and apply the therapeutic properties of resveratrol | Narrative review | RSV's small molecular structure and polyphenolic character endow RSV with antioxidant properties. Beneficial properties of RSV include beneficial effects against tumor processes, cardiovascular parameters, and longevity. However, the concentrations used in vitro are too high to be reached in the organism after red wine consumption. In nutrients containing resveratrol, the results show little biological activity. This is due to the small amount of resveratrol present in natural products and its low bioavailability limits its activity in the target tissues. |

**Table Ib. Properties of RSV**

| Authors, year | Aim of Study | Type of Study | RSV properties |
|---|---|---|---|
| Weiskirchen S and Weiskirchen R (2016) | To discuss the proposed therapeutic attributes and the mode of molecular actions of RSV, to cover recent pharmacologic efforts to improve the poor bioavailability of RSV and influence the transition between body systems in humans | Narrative Review | The bioavailability of resveratrol after oral intake is rather low. Likewise, structural optimization and the development of new galenic resveratrol formulations such as resveratrol-encapsulated nanoparticles should help to physiologically increase resveratrol's activity and overall bioavailability. Resveratrol-enriched supplements might be suitable to allow daily uptake of therapeutically relevant doses (currently presumed to be 1 g) that are not obtainable by conventional foods or beverages |
| Meng et al (2020) | To summarize the main findings of resveratrol-related health benefits in recent epidemiological surveys, experimental studies, and clinical trials, highlighting its related molecular mechanisms | Narrative Review | RSV possesses many bioactivities and health benefits like antioxidant, anti-inflammatory, immunomodulatory effects, and improving cardiovascular diseases, cancer, liver diseases, diabetes, obesity, Alzheimer's disease, and Parkinson's disease. |
| Truong, Jun, and Jeong | To provide current understanding and information on the role of resveratrol in cellular defense systems against oxidative stress. | Article Review | Resveratrol can scavenge both primary ROS/RNS and secondary organic radicals based on HAT and SPLET mechanisms. In addition, resveratrol also modulates several cellular antioxidant pathways, thereby balancing cellular redox status. These contribute to oxidative damage in in vitro models. |
| Fiod et al (2020) | To know the characteristics, biological properties, and analytical methods of Trans-RSV | | anticarcinogenic, antidiabetic, antiacne, antioxidant, anti-inflammatory, neuroprotective, and photoprotector agent |
| Fuggetta et al (2016) | To evaluate the in vitro effect of RES on the production of proinflammatory cytokines | In vitro experimental study | anti-inflammatory activity |

**Table Ic. Properties of RSV**

| Authors, year | Aim of Study | Type of Study | RSV properties |
|---|---|---|---|
| Devi et al (2019) | To investigate the bioavailability and therapeutic effects of RSV | Narrative review | antioxidant, cardioprotective, immunomodulatory, anticancer, antihypertensive, anti-inflammatory and vasorelaxant, antimicrobial, antidiabetic, radioprotective, and neuroprotective activity |
| Ratz-Łyko et al (2019) | To review the effects of resveratrol relating to the physiological processes in the skin | Narrative review | antimicrobial, antiproliferative, anti-inflammatory, anti-angiogenic, antioxidant, skin whitening, anti-acne, estrogen-like effects, and antiaging |

inflammatory cytokines such as interleukin-1β (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and TNF- $\alpha$ were found in the sites of injury. The prolonged inflammatory state in type 1 and type 2 DM is marked by chronic upregulation of pro-inflammatory cytokines such as IL-1, IL-1$\alpha$, IL-4, IL-6, and TNF-$\alpha$. Some researchers stated that there's a substantial number of inflammatory cells surrounding the dermis and vessels of diabetic mice, rats, and rabbits[37,38]. IL-6 is one of the key factors in normal host defense. However, elevated levels of IL-6 are strongly associated with beta cell dysfunction, insulin resistance, hyperglycemia, and chronic diabetic wounds in DM patients[39]. TNF- $\alpha$ is one of the pro-inflammatory cytokines that promote low-grade inflammation. It has a potent neutrophil chemoattractant if compounded with IL-1β and IL-6 and could activate the NF-κB signaling pathways. Overexpression of TNF- $\alpha$ induces fibroblasts, keratinocytes, and endothelial cells apoptosis[40]. Neutrophils have a specific function to produce a large number of reactive oxygen species and proteases which can harm normal tissue. If decreased neutrophils are found, wound healing is more likely to occur in a small amount of time. Deteriorated phagocytic activity and intracellular activity of neutrophils and IL-1β are found in diabetic wounds. Abnormal influx of immune cells in diabetic wounds leads to poor granulation tissue formation and promotes chronic inflammation that interferes normal wound healing process[37]. IL-1β is elevated when there is insulin resistance and a non-healing wound in DM. The anti-IL-1β antibody has been proven to improve beta cell functions in type 2 DM and decrease the IL-6 and TNF-$\alpha$ levels in diabetic wounds[41]. Apart from diabetic wounds, inflammation in a hyperglycemic environment in DM could support the chronic nature of DM. Even the physiologic increases in post-prandial blood glucose could provoke inflammation by activating the pro-inflammatory transcription factor nuclear factor kappa b (NF-κb)[37].

Decreased fibroblast, abnormal keratinocytes, and increased Matrix Metallo-proteinases (MMPs) have also been found in diabetic wounds. Decreased fibroblasts inflicted decreased proliferation, increased apoptosis, and decreased cell migration ability. Abnormal keratinocytes supported wound repair retardation as decreased differentiation and impaired migration ability are found[35]. Increased MMP 1,2,8, and 9 levels might impair the wound healing process as they are components that are in charge of degrading extracellular matrix components such as fibronectin, growth factors, and cytokines[42].

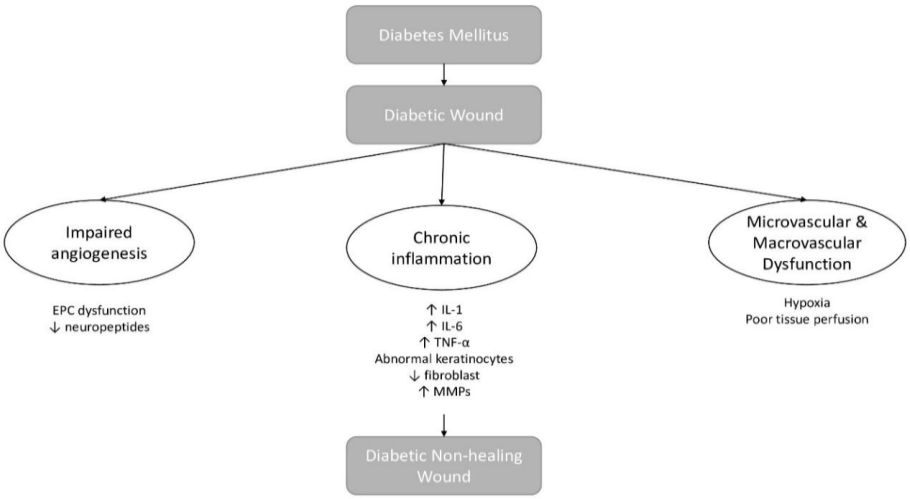
Angiogenesis and vascular endothelial cells are important in the diabetic wound healing process. Most of the cardiovascular complications of diabetes could arise from impaired vasculogenesis and angiogenesis, which are the earliest pathological changes in DM. They are marked by endothelial progenitor cells (EPC) dysfunction, impaired recruitment of EPC from the bone marrow, and decreased neuropeptide levels. The main etiologies of EPC dysfunction are hyperglycemia and chronic inflammation that occur in DM patients[43]. Neuropeptides affect mast cells, endothelial cells, fibroblasts, and keratinocytes activities, therefore decreased neuropeptides could impair the vasculogenesis and angiogenesis in the wound healing process[35].

Microvascular and macrovascular dysfunction in diabetes induces poor tissue perfusion and low oxygen supply, therefore making the environment hypoxic. Hypoxia and chronic hyperglycemia-induced inflammation could elevate the free oxygen radical level and delay the wound healing process[35,44].

**Resveratrol Drug Delivery for Diabetic non-Healing Wounds**

Reviewed from pharmacokinetic parameters, after oral administration of RSV, RSV is absorbed by passive diffusion in the small intestine because of its small and non-polar molecular nature and with a short half-life (8-14 minutes)[29,45]. The liver metabolizes RSV rapidly into sulfated or glucuronidated metabolites. Which then can be recirculated

**Figure 2. Pathogenesis of diabetic non-healing wounds**




and reabsorbed into the small intestine or excreted in the urine[15,29,46]. The aqueous solubility of RSV is known to be low (<0.05 mg/mL), which causes its bioavailability to be low[18,28]. RSV can be utilized in broad fields because of its multiple effects, but it is limited due to its low solubility and bioavailability when administered orally. So, research on oral drug delivery systems in RSV and topical administration through wound dressings has begun to be carried out to overcome these limitations.

*Oral nanoparticles*

In diabetic wounds, there is a condition of chronic hyperglycemia and an increase in ROS, so the wound healing time is relatively longer. RSV is known to have potential hypoglycemic and antioxidant effects for these conditions but is limited due to its low availability when administered orally[47,48]. To improve the oral bioavailability and systemic delivery of RSV, several studies have proven the ability of drug nanoparticle systems. As in the study of RSV encapsulation into solid lipid nanoparticles (SLN-RSV), the results showed SLN-RSV had a more significant glycemic lowering effect than free RSV. Moreover, SLN-RSV encapsulated drug can restore antioxidant levels to nearly normal levels compared to RSV, which only maintains a decrease in antioxidants due to low bioavailability when used orally[49]. Another study by Balata et al. (2016) attempted RSV self-emulsifying drug delivery system (RSV-SEDDS). The results showed that with SEDDS encapsulation, the RSV dose of 10mg/kg had a significant hypoglycemic effect similar to that of 20mg/kg without encapsulation. Thus, SEDDS can optimize the potency of RSV even at lower doses[50]. Adjuvant therapy using RSV can be combined with oral anti-diabetic drugs, as evidenced by a study designed by Bruckbauer et al., (2013), a synergistic effect on insulin sensitivity was obtained from the combination of RSV-metformin (MET)-hydroxymethyl butyrate (HMB)[51]. Another study also obtained the same results that combined RSV with pioglitazone (PGZ)[52]. Thus, in the future, encapsulating RSV nanoparticles with a combination of oral anti-diabetic drugs can become a 2-in-1 drug in treating DM and its complications.

*Modified topical application of RSV: Wound dressing approach*

An alternative to oral drug application is a topical dosage form to prevent the first-pass effect and increase bioavailability. To accelerate the healing of open wounds such as ulcers in diabetic wounds, proper wound environmental conditions are needed. Wound

**Table IIa. Oral drug delivery system of RSV**

| Authors, year | Aim of Study | Type of Study | Type of RSV modification | Summary of results | Advantages | Disadvantages |
|---|---|---|---|---|---|---|
| García-Martínez et al (2021) | To show and analyze the findings on the hypoglycemic effect of different doses of RV from clinical trials and quasi-experimental studies. | Systematic review and meta-analysis | NA | RSV significantly improves glucose and insulin levels in subjects with T2DM and aged 45–59 years, regardless of the duration of the intervention | NA | NA |
| Mohseni et al (2019) | To improve insulin resistance through the upregulation of SNARE protein complex in rats with type 2 diabetes. | In vitro and in vivo experimental study | SLN-RSV | Improvement of insulin resistance through targeting the expression of Snap23, Stx4, and Vamp2 in muscle tissues | Oral administration prevented weight loss showed better hypoglycemic effect than RSV alone | SLV-RSV has a similar effect to RES treatment in adipose tissue |
| Balata et al (2016) | To enhance the dissolution rate and oral hypoglycemic and hypolipidemic effect of resveratrol | In vitro and in vivo experimental study | Rsv-sedds | Treatment with the optimized formula at 10 mg/kg had significant hypoglycemic and hypolipidemic effects in diabetic-induced albino rats which were nearly similar to the high dose (20 mg/kg) of unprocessed resveratrol. | Improvement of dissolution rate and oral bioavailability of resveratrol compared to unprocessed drug | NA |

**Table IIb. Oral drug delivery system of RSV**

| Authors, year | Aim of Study | Type of Study | Type of RSV modification | Summary of results | Advan-tages | Disadvan-tages |
|---|---|---|---|---|---|---|
| Bruckbauer et al (2013) | To determine whether a mixture of the resveratrol, HMB, acts synergistically with low doses of metformin to impact insulin sensitivity and AMP-activated protein kinase-dependent outcomes in cell culture and in diabetic mice. | In vitro and in vivo experim ental study | RSV-MET-HMB | The combination of MET-RSV-HMB significantly increased fat oxidation, AMP-activated protein kinase, and Sirt1 activity in muscle cells | When combined with RSV-HMB, both low-dose and very low-dose MET improved insulin sensitivity ($HOMA_{IR}$), Plasma insulin levels nearly similar to high dose MET | NA |
| Tamimi et al (2023) | To explore the combined use of RSV and established anti-diabetic drug pioglitazone (PGZ) against streptozotocin (STZ)-induced diabetes mellitus (DM). | In vivo experim ental study | RSV with PGZ | Significant decreases in fasting blood glucose, insulin, hba1c and HOMA-IR levels, attenuated lipid disturbances and exhibited an anti-inflammatory effect | Delay DM onset And subsequently minimizes the risk of its related Complication | Pioglitazone causes weight gain, pedal oedema, bone loss, and congestive heart failure in at-risk patients |

NA: not available

**Table IIIa. Modified topical administration of RSV**

| Authors, year | Aim of Study | Type of Study | Type of RSV modifi-cation | Summary of results | Advantages | Disadvantages |
|---|---|---|---|---|---|---|
| Nuutila and Eriksson (2021) | To review the literature on moist wound healing, summarize its benefits, describe currently available moist wound dressing types, and discuss their key characteristics. | Narrativ-e review | NA | Wounds heal faster in a moist environment. | The moist wound environment facilitates autolytic debridement, reduces pain, reduces scarring, activates collagen synthesis, facilitates and promotes keratinocyte migration over the wound surface, and supports the presence and function of nutrients, growth factors, and other soluble mediators in the wound microenvironment | NA |
| Górska et al. (2021) | To prepare hydrophilic active dressings loaded with an anti-inflammatory compound - trans-RSV of hydrophobic properties | In vitro experim-ental study | PVA cryogel membranes loaded with RSV | Less porous and showed higher mechanical strength, able to control the diffusion of RSV for 48 h. | Lowering the ph of FT membranes, which could accelerate the wound healing process | The manufacturing of active hydrogel dressings loaded with poorly soluble active ingredients could be challenging, especially if the membranes of high mechanical resistance, high water uptake and controlled release properties are needed |

**Table IIIb. Modified topical administration of RSV**

| Authors, year | Aim of Study | Type of Study | Type of RSV modification | Summary of results | Advantages | Disadvantages |
|---|---|---|---|---|---|---|
| Gokce et al. (2017) | To develop a dermal matrix consisting of skin proteins and lipids with an antioxidant that will enhance healing and balance the oxidative stress in the diabetic wound area due to the high levels of glucose | In vitro and in vivo experimental study | Collagen-laminin dermal matrix impregnated with rsv-loaded hyaluronic acid-dppc microparticles | The release of RSV was sustained and reached 70% after 6 h. The highest healing score was obtained with the dermal matrix impregnated with rsv-microparticles with increased antioxidant activity. | Synergistic results in the form of increased antioxidant activity, slowing elimination of rsv, with microparticles that can reach the deeper layers, control the release of rsv, and increase tissue | NA |
| Zhu et al. (2022) | To prepare a gelma/SFMA composite hydrogel by adjusting the concentration of SFMA, which was then loaded with two drugs (MSN-RES and pdevs) with different characteristics. | In vivo and in vitro experimental study | Composite hydrogel-loaded RSV-laden nanoparticles and pdevs | Low cytotoxicity and good biocompatibility, inhibited macrophage inos expression and promoted tube formation by human umbilical vein endothelial cells (huvecs) in vitro. In vivo, the gelma/SFMA/MSN-RES/pdevs hydrogels decreased the expression of pro-inflammatory factors TNF-$\alpha$ and inos, increased the expression of anti-inflammatory factors TGF-$\beta$1 and Arg-1, promoted angiogenesis, and accelerated wound healing | Low cytotoxicity, controlled release of RSV, increased angiogenesis, and accelerated wound healing by providing a synergistic effect | NA |

dressing is crucial in the wound healing process because it is a temporary physical barrier to prevent further injury and infection, which can exacerbate the wound[53]. The condition of a wound environment that is moist and clean will support wound healing, and the hydrogel is a platform for wound dressings that are currently widely used to support these conditions[54,55]. Hydrogel has properties that can provide suitable environmental conditions for wound healing, especially chronic wounds, and several other benefits[56]. Górska et al., (2021), designed polyvinyl alcohol (PVA) cryogel membranes loaded with RSV[57], both of them complement each other and form a synergism in chronic wound healing. It was found that PVA cryogel membranes loaded with RSV can control and lower pH to accelerate wound healing and effectively control the release of RSV. Not only could it provide moist conditions and a temporary physical barrier, but also be loaded with a bioactive compound, namely RSV, which can accelerate wound healing through its antioxidant and anti-inflammatory properties[57]. Another study demonstrated a collagen-laminin dermal matrix impregnated with RSV-loaded hyaluronic acid-DPPC microparticles by Gokce et al., (2017), which obtained synergistic results in the form of increased antioxidant activity, slowing elimination of RSV, with microparticles that can reach the deeper layers, control the release of RSV, and increase tissue repair[58]. Zhu et al., (2022), prepared composite hydrogel-loaded RSV-laden nanoparticles and platelet-derived extracellular vesicles (PDEVs) and obtained the outcome in the form of controlled release of RSV, increased angiogenesis, and accelerated wound healing by providing a synergistic effect[59]. To date, no studies have compared the effects of the combinations. Nevertheless, it can be summarized that hydrogel wound dressings have the potential to help improve RSV in wound healing through topical administration.

**Resveratrol and its Roles in Diabetic Wound Healing**

Diabetic wound management faces various challenges as diabetic wounds have keratinocytes hyperproliferative activity, sensitivity down-regulation, and never-ending chronic inflammation. The implication of these complex challenges is the lack of precise treatment targets. The current treatments available for diabetic wounds are debridement and wound care, topical antibiotics, topical dressings, and lifestyle modifications. Therapies that focus on chronic inflammation augmentation, acute immune response, and assistance of dysfunctional immune cells on DM pathophysiology should be the new approaches in treating diabetic non-healing wounds in the future. Plant and its derived products are promising adjuvant therapies to treat diabetic wounds, including RSV[37,60]. RSVs have various biological properties such as antioxidant, anti-inflammatory, and pro-angiogenic activities as they can interact with many targeting molecules and receptors. These properties make them a potential for diabetic non-healing wounds adjunctive therapy[44,61–63]. SIRT-1, a family member of the NAD+-dependent Sir2 histone deacetylases, works to regulate energy homeostasis. RSV can activate SIRT1-1 as it is a possible SIRT1 agonist. SIRT-1 could regulate gene expression as the key regulator of endothelial cell homeostasis, specifically those that are involved in endothelial homeostasis, blood vessel remodeling, and angiogenesis. It contributes to cell proliferation and differentiation process, chemo-preventive and chemotherapy properties in cancer cells, gene silencing, and the aging process[64–66] Another study found that RSV might activate SIRT-1 indirectly via cAMP-degrading phosphodiesterase. Despite the different methods of SIRT1 activation, SIRT-1 could downregulate NF- κB transcriptional activity so that inflammation is decreased and insulin sensitivity is enhanced[24].

**Table IVa. RSV roles in diabetic wound healing**

| Authors, year | Aim of Study | Type of Study | RSV roles in diabetic wound healing | Other results |
|---|---|---|---|---|
| Kulkami and Cantó (2015) | To help understand the impact of Rsv on the general public and the scientific community | Narrative review | Antioxidant, anti-inflammatory, and pro-angiogenic activities | RSV relies on the activation of AMPK and SIRT1. |
| Singh et al (2019) | To summarize the observed clinical effects of resveratrol. | Narrative review | Ability to modulate multiple cell signaling molecules such as cytokines, caspases, matrix metalloproteinases, wnt, nuclear factor-κb, vascular cell adhesion molecule, sirtuin type 1, insulin-like growth factor 1, insulin-like growth factor-binding protein 3, ras association domain family 1α, pakt, vascular endothelial growth factor, etc. | RSV has rapid metabolism and poor bioavailability |
| Pignet et al (2021) | To review highlights the resveratrol-induced molecular pathways with a particular focus on the most relevant variables in wound healing | Narrative review | Pro-angiogenic, anti-oxidative properties, anti-inflammatory potential via the modulation of nf-κb and mapk pathways | Higher concentrations elevate oxidative stress levels and induce cell death. Furthermore, the clinical use of resveratrol is limited by its poor bioavailability and fast metabolism rate |
| Huang et al (2019) | To determine if RES exerts its observed protective role in diabetic wound healing by alleviating hyperglycemia-induced endothelial dysfunction and the disturbance of angiogenesis. | In vivo and in vitro experimental study | Inhibition of hyperglycemia-triggered endothelial dysfunction and a disturbance of angiogenesis, followed by the promotion of diabetic wound healing via RSV | Restoration of the activity of the hyperglycemia-impaired SIRT1 signaling pathway. |

**Table IVb. RSV roles in diabetic wound healing**

| Authors, year | Aim of Study | Type of Study | RSV roles in diabetic wound healing | Other results |
|---|---|---|---|---|
| Zhao et al (2017) | To investigate, by local application, the potential impacts and functional differences of MET, RSV, and RAPA on cutaneous wound healing | In vivo experimental study | Improved vascularization of the wound beds, accelerated wound healing with improved epidermis, hair follicles, and collagen deposition | NA |
| Çetinkalp et al (2020) | To evaluate the efficacy and safety of Dermalix, an investigational medical device, in Wagner 1 and 2 wounds in comparison to a standard wound care (SWC) that consists of irrigation and cleaning with sterile saline solution | Open, prospective, comparative parallel-arm medical Device clinical study | Decreased oxidative Stress in the wound environment | 2 times faster wound healing Properties |

A high amount of FORKHEAD BOXO1 (FOXO1), one of the substrates that interact with SIRT-1, is found in vascular endothelial cells. Increased amount of FOXO1 protein is found in hyperglycemic environments leading to limited angiogenesis activity and hyperglycemia-based apoptosis of microvascular endothelial cells in diabetic rats. RSV has particular properties that could inhibit FOXO1 activity so that endothelial cell dysfunction can be prevented. RSV also decreases c-Myc inhibition as it is bad for the diabetic wound healing process[66,67]. RSV might be a good choice for adjunctive therapy for diabetic non-healing wounds. It not only delays the senescence and hypertrophic scar formation but also exhibits vascular endothelial growth factor (VEGF), therefore tissue regeneration and revascularization in the wound healing process can be assisted[68,69].

Diabetic non-healing wounds could occur as a result of chronic inflammation, oxidative stress, and impaired wound bed perfusion process in diabetic patients. Pro-inflammatory markers such as IL- 1β, IL-6, TNF- $\alpha$, MMP-2, MMP-3, MMP-9, and C-reactive protein (CRP) that delay the wound healing process are found to diminish after RSV is given. As mentioned before, RSV offers a promising antioxidant property that might be beneficial to prevent pathological wound healing processes in diabetic wounds [70–72].

Types of RSV therapy options available for adjunctive therapy for diabetic non-healing wounds are oral and systemic drug delivery. The oral drug delivery system has low bioavailability hence only a scant amount of RSV is accumulated in the target site. Another negative impact of using oral drugs is the systemic side effects that may worsen the disease and its complications. Moreover, RSV is a dose-dependent drug. A higher dose of RSV will cause toxicity while a lower dose added with low bioavailability will lower the drug concentration needed. Adequate drug concentration could be reached if an oral nanoparticle drug system is applied. Drug toxicity would be hindered and there would be enough drug concentration in the target site. Meanwhile, the topical drug delivery system's main approach is adequate wound dressing. Topical RSV in the form of hydrogel is beneficial for diabetic foot ulcer wound dressing as a moist environment and great physical barrier could aid the wound healing process. The antioxidant properties of RSV could also alleviate pro-inflammatory cytokines in chronic inflammation in DM. Moreover, there is diminished drug metabolism that occurs in the gastrointestinal tract hence more concentrated drugs could accumulate in the wound site as higher bioavailability could be approached. Unfortunately, hydrogel is costly. This could compound the already significant burden of DM and its complications that usually impact more than one organ system [70–72].

**Clinical Effects of Resveratrol**

Recently, research related to the effect of RSV as a drug formula has been increasing because of the multi-effect capabilities that have been described previously, especially in metabolic syndromes such as DM. In a previous study by Movahed et al., (2013), 66 patients with controlled T2DM were randomized into the intervention and control groups. The intervention group was given 500 mg RSV capsules twice a day for 45 days. It was concluded that administration of RSV at a reasonably high dose (1g/d) and short-term duration (45 days) was proven to significantly reduce HbA1c, blood sugar, and insulin and insulin resistance, even helping to increase HDL[73]. The same thing was also found in a study by Mahjabeen et al., (2022), with 94 patients with T2DM being given 200 mg/d for 24 weeks and consumed as a supplement to prescribed oral hypoglycemic medications[74]. Other studies regarding the effect of RSV on T2DM are shown in Table I.

Research on RSV as a therapy for non-healing wounds has been carried out by Bashmakov et al., (2014). In this study, 24 patients with controlled T2DM who had newly diagnosed diabetic ulcers were randomized into two groups based on age and sex to receive RSV or placebo. Intervention

**Table Va. Clinical trials of RSV on T2DM and diabetic wounds**

| Authors, year | Aim of Study | Search Database | Type of Study | Subject (No) | Dose, route (duration) | Summary of Results |
|---|---|---|---|---|---|---|
| Movahed et al (2013) | To examine the effectiveness of resveratrol in lowering blood glucose in the presence of standard antidiabetic treatment in patients with type 2 diabetes | PubMed | In a randomized placebo-controlled double-blinded parallel clinical trial. | Patients with controlled T2DM (66) | 2x 500mg/d or placebo, orally (45 d) | Resveratrol treatment significantly decreased systolic blood pressure, fasting blood glucose, haemoglobin A1c, insulin, and insulin resistance, while HDL was significantly increased, when compared to their baseline levels. On the other hand, the placebo group had slightly increased fasting glucose and LDL when compared to their baseline levels. Liver and kidney function markers were unchanged in the intervention group. |
| Mahjabeen, Khan, and Mirza (2022) | To determine the effects of resveratrol supplementation on glucose homeostasis, oxidative stress, inflammation and microRNA expression in patients with diabetes mellitus type 2 on oral hypoglycemic drugs. | Science Direct | Randomized, double-blind, placebo-controlled parallel-group trial with a 1:1 allocation ratio. | patients with T2DM (94) | 200mg/d or placebo, orally (24 wk) | Resveratrol supplementation contributes to the improvement of glycemic control by reducing insulin resistance. It has a significant beneficial impact on chronic inflammation, oxidative stress, and associated microRNA expression in diabetic patients. |

**Table Vb. Clinical trials of RSV on T2DM and diabetic wounds**

| Authors, year | Aim of Study | Search Database | Type of Study | Subject (No) | Dose, route (duration) | Summary of Results |
|---|---|---|---|---|---|---|
| Ma and Zhang (2022) | To investigate the ameliorative effects of resveratrol on blood glucose, insulin metabolism, lipid profile, renal function, inflammation, and nutrient-sensing systems in elderly patients with type 2 diabetes mellitus. | PubMed | a single-blind, parallel-group, randomized controlled clinical trial | elderly patients with T2DM (472) | 500mg/d or placebo, orally (6 mo) | Resveratrol treatment improves inflammation, renal function, blood glucose parameters, inflammation, insulin resistance, and nutrient-sensing systems in elderly patients with type 2 diabetes mellitus |
| Khodabandehloo et al (2018) | To prove that supplementation of resveratrol might improve inflammatory markers in patients with type 2 diabetes mellitus | PubMed | randomized double-blind placebo-controlled clinical trial | patients with T2DM (45) | 2x 400mg/d or placebo, orally (8 wk) | In eight weeks supplementation of resveratrol reduces blood glucose level in patients with type 2 diabetes mellitus without improving their inflammatory markers. |
| Bashmakov et al (2014) | To investigate the effect of a proprietary formulation of trans-resveratrol (t-RSV) on manifestations of diabetic foot syndrome (DFS) in type 2 diabetic patients with newly diagnosed diabetic foot ulcers | PubMed | Placebo-controlled, examiner-blinded, parallel-group randomized controlled pilot clinical trial | patients with controlled T2DM who have newly diagnosed diabetic ulcers (24) | 2x 50mg/d or placebo, orally (60 d) | In RSV-treated patients, there was a reduction in the parameters reflecting diabetic ulcer size, marginally improved performance in the foot pressure test, a statistically significant decline in the plasma fibrinogen level. |

**Table Vc. Clinical trials of RSV on T2DM and diabetic wounds**

| Authors, year | Aim of Study | Search Database | Type of Study | Subject (No) | Dose, route (duration) | Summary of Results |
|---|---|---|---|---|---|---|
| Huang et al (2019) | To determine if RSV exerts its observed protective role in diabetic wound healing by alleviating hyperglycemia-induced endothelial dysfunction and the disturbance of angiogenesis. | PubMed | in vitro and in vivo experimental study | diabetic db/db mice (24) | 50mg/kg/d or placebo, transdermal injection (4 wk) | Resveratrol shows an obvious inhibition of hyperglycemia-triggered endothelial dysfunction and a disturbance of angiogenesis, followed by the promotion of diabetic wound healing, along with restoration of the activity of the hyperglycemia-impaired SIRT1 signaling pathway. |
| Alasmari et al (2018) | To evaluate the potential of topical resveratrol formulation on histological, immunohistochemical, and anti-oxidative findings in experimentally induced full-thickness wound model in induced diabetic rats | Research Gate | in vivo experimental study | diabetic male albino rats (72) | 0,5% ointment or placebo or standard ointment (MEBO 0,25% w/w), topically (3 wk) | Topical resveratrol ointment showed more potential healing effect on diabetic wound than the reference product. Wound treated with resveratrol (group II) showed re-epithelialization and increased epidermal thickness compared with rats in the control group |

**Table Vd. Clinical trials of RSV on T2DM and diabetic wounds**

| Authors, year | Aim of Study | Search Database | Type of Study | Subject (No) | Dose, route (duration) | Summary of Results |
|---|---|---|---|---|---|---|
| Zhou et al (2021) | To observe the effects of resveratrol on oxidative stress impaired cell proliferation, migration, and wound healing in rats. | Science Direct | in vitro and in vivo experimental study | diabetic Male Sprague-Dawley rats (12) | 100mg/mL/d or placebo, topically (2 wk) | In vitro, resveratrol could protect HUVECs against H2O2-induced injury. The scratched wound closed rate in the H2O2 group was significantly smaller than the Control group and Resveratrol + H2O2 group. The fluorescence intensity of ROS was lower in the Control and Resveratrol + H2O2 groups than H2O2 group. In vivo, Resveratrol could significantly accelerate wound healing of rats on Day 14 ($p < 0.05$) and make the regenerated skin structure more complete and inflammatory response lower. |

subjects received 50 mg of RSV orally for 60 days with a frequency of 2 times a day. At the study's endpoint, it was found that the reduction in wound size and decrease in inflammatory mediators (plasma fibrinogen values) were more significant in the observed RSV group. It was concluded that RSV supplementation could be an adjuvant in wound closure therapy of newly diagnosed diabetic foot ulcer patients[75]. In vivo study by Huang et al., (2019), RSV was administered parenterally via transdermal injection at a 50 mg/kg/day dose in diabetic db/db mice. After four weeks, RSV was observed to be able to suppress plasma insulin and fasting blood glucose levels and help accelerate diabetic wound healing when compared to the group of diabetic db/db mice and control littermates group db/m mice which were only given phosphate-buffered saline[66]. A clinical trial with topical RSV administration was carried out by Alasmari et al., (2018), on the subject of 72 diabetic albino rats divided into three groups; control, standard ointment therapy, and topical RSV 0.5% ointment. After being observed at week 3, it was found that only the rats that were given the RSV intervention experienced complete healing. Moreover, in observations using immunohistochemical staining, it was seen that the RSV intervention group was more prominent in the process of forming new epidermal tissue[76]. In another study conducted by Zhou et al., (2021), diabetic rats with burn wounds were cleaned with saline and administered a solution containing 100 mg/mL of RSV topically daily for ten days, and the control group was only cleaned with saline. In week 2, the group with RSV administration was found to experience faster wound healing than the control group, as evidenced by microscopy observations using H&E staining, which showed a milder inflammatory response and more perfect skin regeneration structures[77].

## CONCLUSION

This literature review delivers the pathophysiology of diabetic wound healing and possible pharmacokinetics and pharmacodynamics of RSV as adjunctive therapy for diabetic non-healing wounds to provide information for future research on diabetic non-healing wound treatment. The best option that we found through this literature review is the nano-oral drug delivery system as it could minimize drug metabolism in the gastrointestinal tract, therefore the drug bioavailability and drug concentration on the target site could maximized despite the systemic side effects that could be acquired. There is a dire need for research on novel pathways for treating diabetic non-healing wounds and based on the review written above, properties of RSV might help to prevent diabetic non-healing wound complications in the future.

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