Simvastatin and its application in wound healing and skin disorders: A review

Abstract

Simvastatin is a hydroxy-methyl glutaryl coenzyme A reductase inhibitor, which has been widely known for its lipid lowering effects. Recently a plethora of statins benefits in non-cardiovascular diseases, particularly in wound healing, skin disorders and tissue regeneration have caught attention of many scientists and clinicians. The application of statins in non-cardiovascular diseases is being explored and recently, researchers have begun to recommend statin in the management of skin complications, particularly simvastatin. A substantial \textit{in vitro} and \textit{in vivo} data have shown that topically applied simvastatin possesses anti-inflammatory, anti melanoma, antimicrobial, pro-angiogenesis, lymphangiogenesis and post-surgical cardiac wound healing. Simvastatin appears to exert potential benefits and shows a great perspective for its drug repurposing in wound healing and skin disorder applications. In this review, the various studies of simvastatin in wound healing and various skin disorders are highlighted and discussed. We hope that this review provides valuable insight, stimulates broader concerns, and spurs further developments in this promising field.

Keywords: Simvastatin wound healing, skin disorders, anti-inflammatory, angiogenesis

Introduction

Statins are amongst the most broadly prescribed medicines around the world for cholesterol-lowering with a subsequent risk reduction in cardiovascular morbidity and mortality through lowering the plasma low-density lipoprotein (LDL) level.\textsuperscript{1} Statins are generally considered to be safe lipid-lowering agents with additional pharmacological properties such as blocking leukocyte chemotaxis, lymphocyte activation, antigen presentation, cytokine expression and cellular proliferation. The application of statins in non-cardiovascular diseases is being explored and recently, researchers have begun to recommend statins in the management of skin complications, particularly Simvastatin.\textsuperscript{2} Simvastatin (SIM) is a highly efficient hypolipidemic agent that is categorized under statins class of the drugs. Like many statins, its main mechanism is acting through competitive inhibition of the hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase (liver biosynthetic enzyme) that results in blood cholesterol reduction.\textsuperscript{3} The company Merck & Co., Inc. developed SIM in 1992 and SIM differs chemically from lovastatin only that it has an additional side-chain methyl group (Figure 1).\textsuperscript{4}

![Chemical structure of Simvastatin.](image)

**Figure 1 Chemical structure of Simvastatin.**

SIM is derived from fungus \textit{Aspergillus terreus}\textsuperscript{7} and marketed under trade name Zocor. It became a generic drug in most countries in the year of 2003.\textsuperscript{4} Throughout the years after it was marketed, SIM has been recently reported to have multiple effects apart from its cholesterol-lowering effect, such as anti-inflammatory activity on the skin,\textsuperscript{2} fracture healing,\textsuperscript{6} induction of bone tissue regeneration\textsuperscript{7} and wound healing effects.\textsuperscript{8,9} Therefore, SIM shows evidence that it could be valuable in a diverse application in cutaneous related diseases as well as wound healing.\textsuperscript{10} Some studies reported that topically applied SIM on low doses have beneficial effects.\textsuperscript{10} For instance, one study compared 1% and 3% of SIM ointment and they found that 1% was a more effective formulation for chronic skin inflammation compared to 3%.\textsuperscript{11} In the chronic animal model, SIM ointment 1% was able to reduce ear oedema (25±3%) and ear weight (10±1%), though 3% formulation augmented both parameters.\textsuperscript{12} Another study revealed that high dose of SIM (40mg/kg injected intraperitoneally) to be detrimental and reported loss of VEGF protein expression during skin repairing process.\textsuperscript{13} Many research has been carried out on various topical drug delivery formulations of SIM such as, ointment, lyophilized wafer, film, hydrogel, microemulsion, and gels.\textsuperscript{5,12-15} In this review, we describe the application of SIM in various skin disorders and summarize the recent advances in wound healing effects of SIM with some examples of their application (Table 1). We hope that this review leads to further developments in this new but very promising field for the benefit of human health.

Process of wound healing

Skin, the largest body’s organ offers a protective barrier against the external environment and thus provides vital protective roles to the body. A wound is defined as a state where the normal structure and continuity of body tissue are compromised externally.\textsuperscript{16} Disruption in the skin’s integrity by means of acute or chronic injuries causes the wound healing process to initiatives in order to provide a partial healing for the tissue and repair of the barrier function of the skin.\textsuperscript{17} The process involved in the healing of the wound is considered to be a systematic and complex course (Figure 2) that follows three stages, i.e. hemostasis and inflammation, formation of a new tissue or proliferation and remodeling.\textsuperscript{18}
### Table 1: Summary of studies using Simvastatin application on wound healing effects and skin disorders

<table>
<thead>
<tr>
<th>No</th>
<th>Intervention</th>
<th>Method/subject</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ointment/ Topical Tablet (5mg of simvastatin and 995 mg of petroleum jelly)</td>
<td>SIM in petroleum jelly or petroleum jelly alone were applied separately on the wound created on back of the diabetic mice</td>
<td>Stimulation of lymphangiogenesis was observed on diabetic wounded mice&lt;sup&gt;42&lt;/sup&gt;</td>
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<tr>
<td>2</td>
<td>Intra peritoneal injection (5 mg/kg)</td>
<td>SIM was administrated on diabetic mice possessing an Incisional wound</td>
<td>Enhancement in production of VEGF mRNA, protein expression, augmented nitric oxide contents, enhanced skin’s breaking strength and restored the impaired wound healing process.&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Simvastatin microemulsion (10 g/mL)</td>
<td>An open wound was created on the dorsal of the rats then infection was induced by multi bacterial solution of rats feces and saline</td>
<td>Enhanced inflammatory reactions and Reduction in infection.&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Simvastatin tablet (40 mg)</td>
<td>Sixty-six patients suffering from venus ulcer were treated with SIM on daily basis during bedtime for 10 weeks or shorter if healed earlier</td>
<td>The healing rate was enhanced and period of healing was reduced (both significantly).&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>SIM gel (2%)</td>
<td>Full thickness wound was created on the posterior surface of animal’s neck then formulation or vehicle was applied individually</td>
<td>SIM therapy enhances the healing process targeting various aspects of tissue regeneration, anti-inflammatory, epithelisation, the proliferation of fibroblasts and collagen synthesis.&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>SIM ointment (1% or 3% w/w)</td>
<td>SIM was tested against various gram-positive and negative bacterial strains (in-vitro) and applied on wounded mice induced MRSA infection (in-vivo)</td>
<td>Exhibited broad-spectrum antibacterial activity against important Gram-positive (MRSA) and gram-negative pathogens. The infected wound was shown with lowered bacterial burden and inflammatory cytokines and showed excellent antibiofilm activity.&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>SIM solution (62.5 and 125 μg/mL)</td>
<td>MIC of SIM against S. aureus, anti-biofilm, and effectiveness of SIM against S. aureus microorganism treated mouse excisional wound was studied</td>
<td>Topical application of SIM at its MIC against S. aureus was effective and accelerated management of S. aureus wound infection and its antibiofilm activity was concentration dependent.&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Oral SIM (0.25 mg/ kg)</td>
<td>Nude mice were pre-treated with SIM on daily basis and excisional skin wound was created after diabetic induction to evaluate angiogenesis and wound healing effects</td>
<td>Low dose SIM pre-treatment may increase neutrophil infiltration, increase VEGF production and enhance healing of the diabetic wounds.&lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>SIM and other statin tablets (atorvastatin, rosuvastatin, pravastatin)</td>
<td>139 human subjects between 18-80 years with DFUs were treated with SIM or several other medications over 6 weeks of therapy to see the wound reduction effect</td>
<td>The outcome showed that the subjects taking statins were more likely to have wound size reduction at 6 weeks of therapy.&lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>SIM ointment formulation in 1% and 3% (w/w)</td>
<td>Topical application of SIM in acute and chronic skin inflammation in mice was tested then oedema was evaluated every day by measuring the increase in ear thickness</td>
<td>The anti-inflammatory action of SIM in both acute and chronic inflammation models was confirmed, however, SIM ointment in 1% revealed to be a very effective for the chronic skin inflammatory application.&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Topical application of SIM</td>
<td>SIM treatment was evaluated in mice models with skin inflammation and compared with dexamethasone as a control in acute irritant contact dermatitis</td>
<td>Prevention of oedema formation and migration of polymorphonuclear leukocytes, also inhibition of erythema suggesting topical anti-inflammatory effects of SIM.&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Oral administration of SIM solution (5–30 mg/kg)</td>
<td>Anti-inflammatory effectiveness of SIM was compared to the control in the carrageenan-induced rat paw oedema test</td>
<td>Dose dependent anti-inflammatory activity of SIM was evident and it was equivalent to that of control where the efficacy was highest by the maximum applied doses.&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>SIM (0.3 mg/ear ) and other statins were applied topically</td>
<td>The topical anti-inflammatory effectiveness of SIM was measured in ear oedema in mice model and compared to other statins</td>
<td>SIM resulted in highest reduction (79%) in ear oedema compared to other statins and demonstrated topical anti-inflammatory effects.&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>Topical and systemic SIM application</td>
<td>Immunomodulatory activity of SIM as a topical or systemic host-directed drug therapy in mice model of skin leishmaniasis caused by Leishmania major was evaluated</td>
<td>SIM administration increased host protection against Leishmania major by enhancing the macrophage phagosome maturation and killing effector.&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
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Figure 2 The process of wound healing.

Haemostasis and inflammation

The first stage in the healing of the wound begins with hemostasis and then inflammation, where it lasts until about 2 days after the tissue injury. Here, the constituents of the clotting cascade, the inflammatory pathways, and immune system are necessary to counteract ongoing blood and loss of the fluids. Hemostasis is attained by coagulation followed by a fibrin matrix that gives the fundamental building block to initiate the inflammatory phase and tissue structuring. Next, the cellular inflammatory stage follows in order to form an immune barrier against attacking micro-organisms. Inflammatory stage triggers by the arrival of the blood cells like, phagocytic neutrophils and then macrophages at the wound site. Initially, the foreign particles are removed by phagocytes, also, liberating cytokines to stimulate fibroblast migration and proliferation to the end of this stage. It is worth mentioning that, the inflammatory response after the injury has a critical function in both normal and pathological healing that begins moments after an injury as the innate immune system is triggered, stimulating the local inflammatory response. A skin wound at about 1 to 2 days after injury is shown in Figure 2A.

New tissue formation or proliferation

After about 2 to 10 days from the wound’s injury this phase occurs. During this phase, the wound’s defect is packed with a very vascular connective tissue, suggested as ‘granulation tissue’. At this stage, the wound atmosphere has a low level of pH, low oxygen tension and added lactate as an outcome of a vascularity’s loss in the wound bed. This phase is characterized by the migration of keratinocytes over the injured dermis, establishment of new blood vessels (angiogenesis), synthesis of extracellular matrix constituents such as collagen, formation of granulation tissue, re-epithelialisation and scar formation on the wound’s surface. A wound environment at about 5 to 10 days after injury is shown in Figure 2B.

Remodeling or maturation

This phase initiates 2 to 3 weeks after the tissue injury and continues for almost one year or longer. At this phase, each of the events triggered after the tissue injury taper off, leaving a bulk that comprised of few cells and contains mostly of collagen and other extracellular matrix proteins. Depicted (Figure 2C) is a wound of about 1-12 months ago after repair process. This gradual course growths the tensile strength of the wound, however, the scar tissue is certainly not more than 80% of the tensile strength in non-wounded tissue. This phase encompasses the development of cellular connective tissue and establishment of the new epithelium which controls the kind of the final scar.

Role of simvastatin in dermal disorders and wound healing

A principal site for the cholesterol biosynthesis is the epidermis, which is governed by barrier function. Many researchers have focused on the positive effects of statins on the process of the wound healing. SIM, besides being a lipid-lowering agent, also found to be advantageous for wound healing and regeneration of tissues. Table 1 gives the summary of studies carried out using SIM on wound healing and various skin disorders. The following sections discuss the potential and recent roles of SIM in wound healing process and its application on skin disorders as well as the benefits of SIM in the skin and wound care.
Anti-inflammatory effects

The inflammatory response after an injury has a critical function in both normal and pathological healing. It begins moments after an injury as the innate immune system is triggered, stimulating the local inflammatory response that involves the recruitment of inflammatory cells from the circulation of the blood. For the past decade, SIM has been researched for its anti-inflammatory roles. The anti-inflammatory effects of statins involve cutting the C-reactive peptide release and declining in cytokines, chemokines, and adhesion molecules, also, regulating of T-cell activity. Adami et al., evaluated the topical effects of SIM as ointment formulations. 1% and 3% (w/w) of SIM ointment were applied and compared to the dexamethasone ointment (as a positive control) in the skin inflammation models. They found that a potent anti-inflammatory response was produced when SIM was applied topically on acute or chronic wounds on the mice models. For the acute usage, both percentages were effective in reducing skin inflammation whereas; in chronic model, SIM ointment 1% demonstrated to be a more efficient formulation. The study also found that 1% SIM ointment vehicle preserved its anti-inflammatory activity and prohibited the issues related to the skin barrier disruption which was spotted with 3% SIM ointment. The anti-inflammatory activity of SIM inhibited development of oedema and migration of neutrophils that were confirmed by the MPO enzymatic activity (as a marker for tissue neutrophil content) and histological analysis. As the neutrophil’s accumulation shows a serious function in the skin inflammatory diseases such as, psoriasis and dermatitis, and statins prevent the inflammatory cells infiltration in a dose-dependent manner, thereby they concluded that SIM could be a medication for dermatologic diseases.

Another study by Otsuki and colleagues evaluated the topical anti-inflammatory efficacy of SIM in mice that were treated with croton oil model of skin inflammation and compared with dexamethasone as a control. Topical application of SIM caused an obvious inhibition of oedema growth and migration of polymorphonuclear leucocytes compared to the anti-inflammatory drug. Additionally, SIM triggered a noticeable prevention of the erythema 6 hours after applying the croton oil and demonstrated that topically applied SIM had an anti-inflammatory properties in acute irritant contact dermatitis. Local anti-inflammatory effect of SIM was studied on a carrageenan-induced footpad oedema, as a standard model of an acute local inflammation. The prevention of footpad swelling of this model delivers a well-characterized scale of an anti-inflammatory action. In this testing, it was revealed that SIM formed apparent anti-inflammatory activity equivalent to that of indomethacin where the strength and efficacy of SIM in this model were dose-dependent, with a highest effect attained by the maximum applied doses. Anti-inflammatory activity of topically applied SIM, pravastatin, atorvastatin, ezetimibe and combination of SIM and ezetimibe was investigated by Bracht and co-workers, using croton oil model of ear oedema in mice model. The inhibition of ear oedema was found to be 79%, 67% and 40% for SIM, atorvastatin and pravastatin, respectively. Moreover, it was also determined that statins can act as topical anti-inflammatory formulation, however, the pharmacological outcomes are related to the statin’s polarity.

In a research on inflammatory effects of statins it was reported that, statins show a decrease in the interaction of inflammatory mediators such as C-reactive protein, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), the endothelium-leukocyte and monocyte chemoattractant protein-1 (MCP-1) which was evident by the growing clinical studies. Owing to the fact that, many skin related complications such as psoriasis and contact dermatitis, bullous pemphigoid, alopecia areata, and lichen planus, were recognized by the occurrence of inflammation and extreme lymphocyte infiltration, statins might be a significant add-on to the dermatological anti-inflammatory treatment resource. Recently a novel therapeutic potential of the SIM was reported when used topically on cutaneous leishmaniasis in mice. The researchers confirmed the reduction in the tissue damage and parasite burden in lesions caused by L. major after topical application of simvastatin. Furthermore, when investigated for its prophylactic potential, SIM exhibited host protective effects, which reduced footpad swellings and parasite burdens in mice.

Antimicrobial effects on infected wounds

One of the contributing factors in delaying the wound healing process is the wound infection and the prolonged wound infections are expensive to treat. It is stated that, in hospitals around the world, development of wound infection takes place in 2-5% of patients undergoing a surgery every year whereas, it continues to be regarded as one of the main glitches in surgical wards currently. Statins, particularly, SIM, have the potential to be repurposed as new antibacterial agents on the basis of the preliminary studies performed so far. Also some studies, indicated that SIM possessed antibacterial properties against various microorganisms when tested in vitro.

One study demonstrated the potential role of a topical microemulsion containing SIM on open infected wounds in the rat model. The animal models were divided into 2 groups, one received topical SIM microemulsion and the other group received 0.9% saline solution. Immunohistochemical staining of the tissue samples for TNF-α and IL-1β, histopathology and bacteriological examination was performed. The results revealed that expression of TNF-α was found to be lower in skin wounds treated with SIM than in saline-treated wounds, IL-1β expression was also notably improved in the group treated with saline than in the group SIM treated group after the full epithelialization of the skin wounds. In addition, histopathology analysis revealed that leukocyte infiltration was notably lower than that spotted in the saline group. Four days after the wound’s treatment, the bacteriological testing of the samples obtained from wound’s fluid revealed the presence of wound infection in one rat of the group treated with SIM, whereas, polymicrobial infection was detected in all the wounds. They concluded that the SIM microemulsion when applied topically diminished the inflammatory response in wound healing of infected tissues.

The efficacy and safety of SIM tablet was carried out clinically by another study in venous ulcer healing when combined with standard therapy (compression therapy) for the venous ulcer. It was revealed that, SIM tablet (40mg/day) in addition to standard wound care and compression therapy showed a substantial improvement in healing rate and time, moreover, patient quality of life was enhanced when compared with placebo in the controlling the venous ulcers. In the SIM group, 90% of patients showed full ulcer closure in comparison to the 34% in the control (placebo) group. Overall, SIM was shown to be more effective compared to the placebo in controlling the venous ulcers based on a higher proportion of healed ulcers, shorter duration of healing and a better quality of life. Therefore, this can be justified by venoactive and nonvenoactive characteristics of statins where as, compression alone will provide only venoactive management of the disease. The Infectious Disease Society of America has called for the development of new efficient antimicrobial agents working on several species, of which S. aureus is a significant member, by 2020. The
World Health Organization has also announced its concerns about the rise of antimicrobial resistance, therefore, drug repurposing has been explored as a potential strategy against *S. aureus* infection using a number of US FDA-approved and non-antimicrobial drugs for their potent anti-staphylococcal activity.39

As a matter of fact, *S. aureus* is a reason for many of the skin related infections in humans, therefore, there is a potential for using SIM to prevent/treat bacterial infections in wounds based on the reported studies. Thangamani et al.,30 evaluated the anti-staphylococcal activity of SIM to assess its topical effect on *S. aureus* contaminated cutaneous wounds as one of the chief microorganisms accountable for wound infections. To assess the influence of SIM on the wounds contaminated with *S. aureus*, mice excisional wound infection model was employed then, it was revealed that, SIM had bacteriostatic characteristics towards *S. aureus* and this effect was apart from its HMG-CoA reductase inhibitory action.30 According to Wang et al.,31 topical SIM treatment had the potential as a wound care modality for inhibiting or treating *S. aureus* related infections of wound. It was reported that, the antimicrobial properties of SIM was depend on the organisms examined.31 They highlighted that, topical SIM application promotes healing and bacterial clearance of *S. aureus* contaminated wounds via several steps, including direct antibacterial activity, inflammation modulation and promoting wound healing.35

Thangamani et al.,30 examined eight different statins including SIM for their topical antibacterial effects and evaluated the range of action on both gram-positive and negative bacterial species. They reported that only SIM exhibits broad-spectrum of antibacterial action against gram-positive bacteria comprising MSSA, MRSA, VISA, VRSA and VRE at 32mg/L. With regards to the gram-negative pathogen, they claimed that in gram-negative bacteria, outer membrane acts as an intrinsic barrier for SIM to get the access, therefore, ineffective against gram-negative bacteria. Additionally, they evaluated the efficacy of SIM as a topical antibacterial in an infected skin of the murine model (MRSA-infected mice). SIM, in both at 1 and 3% concentration, decreased the mean bacterial counts and inflammatory cytokines (IL-1β, IL-6 and TNF-α) significantly in comparison to the control group.30

Besides, SIM was able to disturb adherent staphylococcal biofilms capable of being used in conjunction with other topical antimicrobials presently used (vancomycin) for the skin infections treatment.30 Also, the MIC of SIM against *S. aureus* 29213 was reported to be 15.65mg/mL and 31.25mg/mL for the other strains of *S. aureus*.36

**Anti-melanoma effects of simvastatin**

Besides the common usage of statins in the management of hyperlipidemia disorders, statins have been investigated for their anti-carcinogenic properties. One of the dangerous kind of the skin cancer is malignant melanoma and the prognosis of those with metastatic malignancy is found to be weak.37 It was reported that, contrarily to the non-cancerous cells, cancerous cells, comprising melanoma cells, utilize the cholesterol. Such findings have raised the hypotheses that medications adjusting the cholesterol levels may slow or stop tumor growth, improve the anticancer activity of chemotherapy, or probably inhibit cancer.38 The anti-proliferative properties of SIM on the growth inhibition of melanoma cell progression in vivo were studied by Zanfardino and co-workers.37 They disclosed that administration of SIM stimulated morphological changes and diminished tumor cell proliferation. They also reported a delay in the development of the tumor in almost 50% of the SIM treated animals and a high reduction (150%) in the tumor’s volume in comparison to the controls. Besides, the rate of animal survival was notably more in those mice models that were administered the drug with a survival rate increase of around 130%. They concluded that, the inhibition in the growth of cancer cells were due to the deregulation of apoptosis induction and also prevention of the expression of the gene nuclear p54
tk protein.

Saito and co-workers evaluated the anti-tumor effect of SIM on human melanoma cell lines where, the cells were treated with SIM in various concentrations (0.5, 1, 2.5, 5, 10, and 15 mmol/L) for 1-3 days. The cell viability, morphologic changes, and reversibility of inhibition by geranylgeranyl pyrophosphate and farnesyl pyrophosphate, apoptosis, and the cell cycle were tested. The results indicated that SIM had anti-proliferative activity, and this effect was somehow due to the induction of apoptosis and a cell cycle arrest. Therefore, they recommended that, SIM could be an potential active anticancer agent for malignant melanoma.38 Another study tested statin drugs to see if they have inhibitory activity on proliferation of melanoma cells, migration and invasion. They found out that there was an inhibition in the proliferation of melanoma cell lines when treated with SIM and suggested that melanoma could be sensitive to statin administration. Besides, SIM was also found to prevent melanoma cell invasion in a dose-dependent mode. Their results specified that the standard dosage normally used for cholesterol lowering effects might not be adequate to directly prevent melanoma cell proliferation or invasion. However, statin treatment at greater doses might may be useful as an adjuvant therapy to inhibit melanoma cell growth, invasion, and metastasis.39

A metanalysis study using randomized controlled trials involving 62,568 individuals was carried out to assess if statin administration declines with the risk related to melanoma. Despite past literatures supporting the beneficial of statins in melanoma treatment (*in-vitro* and *in-vivo*), they reported that the quantitative synthesis of sixteen randomized clinical trials gave no supporting results for any connection between statin usage and the risk of melanoma. All an all, it was stated that statins treatment at low doses for the management of hypercholesterolemia did not provide protective effects against melanoma but, a modest reduction in risk or an effect linked with greater doses cannot be eliminated.41

**Angiogenesis, VEGF production and lymphangiogenesis effects of simvastatin**

An ideal wound healing agent not only to accelerate wound healing, it should also provide protection against wound’s infection, lowering the inflammation and enhance cell’s proliferation in order to heal or regenerate the damaged tissue. One of the critical factors in wound repair is the reformation of a functional vascular network and formation of the new blood vessels to supply the hypoxic wound bed is, angiogenesis which is highly complex and tightly regulated.42

Angiogenesis is augmented by vascular endothelial growth factor (VEGF) as a vital pro-angiogenic agents which is a matricellular protein produced by keratinocytes, and macrophages during the early phases of physiological wound repair, resulting in increased vascular permeability, endothelial cell migration, and capillary formation.43 A study was conducted on laboratory rats to analyze the effectiveness of SIM on the process of wound healing by using histopathological and stereological evaluation. Rat models were allocated into 3 groups; group one was treated with a topical SIM gel (2%); no treatment was given in group two, irrigation with normal saline were employed on daily basis and animals in the group three were administered with the gel base alone. After completion of the course, results revealed that,
SIM was shown to improve healing process by the virtue of its anti-inflammatory and epithelization generation, induction of fibroblast proliferation and synthesis of collagen bundle.\(^4\)

The effect of SIM treatment on type 2 diabetic mice skin wound defects was investigated by Bitto and coworkers (2008).\(^3\) The mice models were treated everyday with SIM (5mg/kg i.p.) or vehicle alone and the measurement was carried out on VEGF mRNA and protein expression, to determine histologically the wound healing activity and to assess the wound breaking strength and angiogenesis by CD31 immunostaining. The outcome revealed that, SIM application in diabetic mice boosted VEGF mRNA, protein expression and improved the content of nitric oxide in the wound at day 6 and enhanced breaking strength and PECAM-1 immunostaining at day 12. They reported that SIM was capable of increasing the altered pattern of production and secretion of VEGF in mutant’s diabetic mice. Besides, SIM clearly enriched the altered wound repair in diabetic mice and this positive effect was entirely abrogated by a passive immunization with an anti-VEGF monoclonal antibody, strongly proposing that the SIM-promoted improvement in skin repair could be mediated by VEGF.\(^7\)

It is stated in the literature that, nitric oxide (NO) is a regulator of VEGF expression.\(^4^4\) One study stated the enhanced nitric oxide in wound samples obtained from SIM administered animals, supporting the postulation that nitric oxide and its metabolites could somehow represent, one of the vital pathways involved in SIM-induced VEGF release or, alternatively, an effector mediator of VEGF-related effects.\(^3\) Matsuno et al.\(^\text{45}\) investigated the crucial role of SIM following an endothelial injury in male hamsters.\(^4^6\) They concluded that SIM possessed a key local physiological function in vascular remodeling and improvement of the vascular potency following an endothelial injury, that was the consequence of the regeneration of endothelial cells through an over release of VEGF.\(^4^7\) Recently the proangiogenic properties of SIM in a hamster model with hind limb ischemia was assessed after oral treatment of SIM for was carried out for 28 days. The immunohistochemical results on VEGF expression showed that SIM significantly augmented tissue VEGF expression from day 8 with an increase in capillary density from 14th day .\(^4^8\)

Asai et al.,\(^4^9\) have demonstrated that topical applications of SIM augments lymphangiogenesis and angiogenesis in diabetic wounds in animal model. For this purpose, SIM ointment in petroleum jelly or petroleum jelly alone was used as control. Capillary morphogenesis of lymphatic endothelial cells was significantly stimulated by SIM as an effect on vascular endothelial cells that was, at least in part, regulated by the AKT/Pi3K/mTOR pathway. In this study, the number of infiltrating macrophages in granulation tissue was highly increased by topical administration of SIM, and most of these macrophages produced VEGF-C. The results revealed that SIM recovers lymphangiogenic function that was impaired in macrophages under diabetic conditions. This study suggested that topical SIM can stimulate lymphangiogenesis by directly acting on lymphatics and indirectly via stimulation of macrophages and topical SIM might be a new healing approach for the treatment of local ischemic conditions, such as those in patients with diabetic ulcers.\(^5^0\)

Cardiac (post-surgical) wound healing effects of simvastatin

The numbers of the cardiac patient undergoing surgical practice have often linked to comorbidities that can obstruct a wound healing process (postoperative). This has greatly affected patient quality of life and imposes a significant wound care cost.\(^5^1\) A systematic review was conducted by Fitzmaurice et al.,\(^1\) to assess the potential for statins in postoperative wound healing. They reported that there was sufficient evidence at present to merit a randomized controlled double-blind clinical trial to systematically measure the function of statins in the treatment of postoperative wound healing. They considered that statins administered topically, offers the prime mode of administration and, hence could be considered as the initial delivery mode to be assessed for human benefit. They also stated that lipophilic statins appear to have the most potential due to previously documented advantageous in the induction of fracture healing, and certainly, atorvastatin and SIM were the most extensively explored statins throughout their research.\(^1\)

**Conclusion**

In this review, we have discussed the SIM applications on wound healing and skin disorders including its anti-inflammatory, anti-melanoma, pro-angiogenetic and lymphangiogenesis and cardiac (post-surgical) wound healing effects. Some of the latest developments in the practical antibacterial applications of SIM have also been reviewed. The substantiate data obtained from both animal and human studies have suggested that SIM exhibits potential therapeutic efficacy in the wound healing and cutaneous disorders. SIM also showed promising therapeutic responses via topical route other than oral administration warrant the need to develop an effective and stable topical delivery system for SIM. Although, the topical therapy by SIM is already established for different diseases, but further research is required to determine the optimal therapeutic dose for long-term treatment where the prime result can be exerted on them.

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None.

**Conflicts of interest**

We declare that there is no conflict of interest regarding the publication of this article.

**References**


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