REVIEW

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Beneficial effects of simvastatin in wound healing: review of the literature

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ABSTRACT

Wound healing is a complex, natural biological, and dynamic process or loss of cellular structures, tissue layers, and replacing damaged tissue. Molecular responses, cellular components, and humoral components are healing process that occurs in hemostasis, including inflammation, proliferation, and remodeling. In order to achieve good healing, these four steps must be performed in the right order and at the right time. In recent years, research has shown that simvastatin has pleiotropic properties that have been linked to improved wound healing in experimental animals and humans. However, higher-quality and evidence-based research is needed to determine the duration of treatment, the best method of administration, the correct dose, and to relate the pleiotropic properties of simvastatin to its potential therapeutic.

Keywords: simvastatin, wound, wound healing.
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INTRODUCTION

A wound may be a circumstance where the coherence of the tissue (epithelial skin and basic tissue) is hindered because of different things comprising of mischances, injury, or surgical operation.[1] Hemostasis, infection, proliferation, revascularization, and reworking are all part of the wound recovery method.[2,3] Wound rebuilding issues are occurrences that we frequently experience within the day-by-day workout since of oxidative stretch, proteolysis, and the aggregation of harmful chemicals that emerge all through aggravation, inflammation is one of the most thought processes for deferred wound recuperation.[2,4] Advance bacterial contamination too can restrain wound rebuilding with the help of interferometer with angiogenesis and discharge of plasminogen activator and proteolytic proteins.[2] Through a long time, there have been numerous makes utilize of topical or possibly systemic anti-microbials to treat wound diseases. Various requesting circumstances inside the utilize of anti-microbials comprehensive of aspect results and resistance issues make the require for brand beating unused pharmaceutical stock for wound mending an expanding number of imperative.[5] Directly, simvastatin may be a novel treatment option for a repercussion of neurotic ailments, together with psoriasis, sepsis, alopecia, wound rebuilding, and other fiery illnesses, since its pleiotropic impacts assist to its lipid-lowering movement.[2,6,7] Simvastatin has differing pleiotropic impacts counting, reperfusion, immunomodulatory, antibacterial, anti-antioxidative, provocative, advanced microvascular work, and angiogenesis, as well as the impact of quickening the wound rebuilding prepare.[2,3,8-10] The impacts of statins on wound reclamation in current clinical and non-clinical trials have been inspected in this review.

METHODS

The keywords simvastatin and wound healing were used to search the literature in PubMed, Medline, and Science Direct databases. Articles with pertinent titles and abstracts were included. All ponders that looked at the impact of statins on wound recuperating as an essential surrogate result were included. Several animal and human research have proposed that the wound healing process be enhanced.[2,3,10-16]

SIMVASTATIN

Simvastatin is one of the statin families that is fundamentally used to bring down blood cholesterol.[17,18] Aside from the cholesterol-bringing down impact, it has been shown that simvastatin has a few helpful activities, one of which is the capacity of simvastatin to expand VEGF (Vascular Endothelial Growth Factor) blend and delivery at the injury site, which is a basic advance in the arrangement of fresh blood vessels and, subsequently, further develops disabled injury recuperating in diabetic mice.[3,19] Simvastatin stimulates wound closure in human ex vivo culture and keratinocyte motility in vitro by bringing down farnesyl pyrophosphate (FPP) and isoprenylation downstream targets of mevalonate.[20] In a rodent excision demonstration, Rego et al. stated topical simvastatin with 10 mg/ml microemulsion decreased wound worsening, bacterial stack, and leukocyte attack compared to standard saline.[13] Karadeniz Cakmak et al. showed in an animal model the use of simvastatin in anastomotic wound recovery made progress in re-epithelialization, reduced the granuloma action process, reduced scorching attack into the muscle layer, and reduced ischemic deterioration, illustrated

by histopathological examination. It produced an important mechanical and biochemical patch with no anastomotic spills or septic complications compared to the control group.[14] Simvastatin shows up to have an extraordinary strong potential for overlay survival due to its overexpression of thrombomodulin at the surface of vascular endothelial cells, updated cutaneous circulatory system, and diminished microthrombus course of action highlights.[15] Ramhormozie et al., In their rats model, stated that the topical application of SMV advanced the patch formation of severe second-degree burn wounds by aligning characteristic natural shapes, updating re-epithelialization, capturing angiogenesis, increasing collagen formation, and improving the function of granulation tissue.[3] Khoshneviszadeh et al. stated that simvastatin has anti-inflammatory to promote wound healing and epithelizing effects, as well as the very basic activation of collagen and fibroblast growth.[21] Rayinda et al. stated topical simvastatin in patients with systemic scleroderma might speed up treatment recovery from persistent ulcers by reducing farnesyl pyrophosphate levels, promoting vasoconstriction, accelerating neovascularization, and lowering bacterial counts.[22] Jia et al. it appears that topical treatment with simvastatin reduces the scar in an approved rabbit ear scar, as demonstrated by an interferometer with mRNA expression of the connective tissue developmental figure.[23] Masadeh et al. found that simvastatin is successful against methicillin-susceptible Staphylococcus aureus, methicillin-resistant Staphylococcus aureus, or other microorganisms normally found in wounds such as Acinetobacter baumannii, Staphylococcus epidermidis and vancomycin-sensitive and safe enterococci.[24-26] Wang et al. appeared that topical simvastatin might be a promising approach to prevent and control S. aureus wound contamination in different ways, considering the coordinated antibacterial activity, burn direction, and promotion of wound healing.[26] In agreement with Asai et al., topical application of simvastatin quickened the mending of diabetic wounds by a progression of angiogenesis and lymphangiogenesis.[27]

CONCLUSION

Aside from the effect of lowering blood cholesterol levels, simvastatin is considered a promising candidate for accelerating wound healing by promoting planning of angiogenesis and progress in epithelization, even though proof of simvastatin's possibly advantageous impact on wound mending is to a great extent creature-based one considers with little test sizes and short-term follow-up. On the off chance that simvastatin is profitable in a clinical environment for progressing wound recovering, and whether long-term simvastatin medication is fitting for putting off or keeping up a vital separation from wound compounding, are issues that have to be that as it may be settled in largescale clinical considers. Simvastatin can diminish the bacterial improvement of gram-positive germs, so to talk, which can offer assistance within the treatment of sullied wounds; it can moreover be managed topically as a hydrogel to help in recuperating without causing systemic harmfulness. Even though simvastatin has appeared advantageous impacts in creature considers in a few sorts of wounds such as degenerative, ischemic, anastomotic, and diabetic wounds. Additional research is needed to compare the healing effects of statins on different wounds.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to this article.

REFERENCES

1. Atmodiwirjo P. Understanding the phases of wound healing for the best resultant scar. In: Sudjatmiko G, Sukasah CL, Susanto I, editors. Advanced Suturing Skills How to Stich Like a Plastic Surgeon. 1st ed. Jakarta:Yayasan Lingkar Bedah Plastik;2013:p5-18
2. Farsaei S, Khalili H, Farboud ES. Potential role of statins on wound healing: a review of the literature. *Int Wound J*. 2012;9(3):238-247.
3. Ramhormozi P, Ansari JM, Simorgh S, Asgari HR, Najafi M, Barati M, Babakhani A, Nobakht M.Simvastatin accelerates the healing process of burn wound in Wistar rats through Akt/mTOR signaling pathway. *Annals of Anatomy*.2020:1-34
4. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *Journal of Investigative Dermatology*. 2007;127(3):514–25.
5. Sevgi M, Toklu A, Vecchio D, Hamblin M.Topical Antimicrobials for Burn Infections: An Update. Recent Pat *Antiinfect Drug Discov*.2014;8:161-97.
6. Corsonello A, Garasto S, Abbatecola AM, Rose G, Passarino G, Mazzei B, Pranno L, Guffanti EE, Bustacchini S, Lattanzio F. Targeting inflammation to slow or delay functional decline: where are we? *Biogerontology*.2010;11(5):603–14.
7. Libby P OY, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. *Circ J*.2010;74(2):213–20.
8. Adam O, Laufs U. Antioxidative effects of statins. *Archives of toxicology*. 2008;82(12):885–92.
9. Hennessy E, Adams C, Reen FJ, O'Gara F. Is There Potential for Repurposing Statins as Novel Antimicrobials? *Antimicrob Agents Chemother*. 2016;60(9):5111-21.
10. Bitto A, Minutoli L, Altavilla D, Polito F, Fiumara T, Marini H, Galeano M, Calo M, Lo Cascio P, ` Bonaiuto M, Migliorato A, Caputi AP, Squadrito F. Simvastatin enhances VEGF production and ameliorates impaired wound healing in experimental diabetes. *Pharmacological Research*. 2008;57(2):159–69.
11. Sameh N, Aly UF, Abou-Taleb HA, Abdellatif AAH. Prospective Role of Simvastatin on Wound Healing: Review of the Literature. *J Bioequiv*.2018;10(2): 36-42.
12. Raposio E, Libondi G, Bertozzi N, Grignaffini E, Grieco MP. Effects of Topic Simvastatin for the Treatment of Chronic Vascular Cutaneous Ulcers: A Pilot Study. *J Am Coll Clin Wound Spec*. 2016;7(1-3):13-8.
13. Rego AC, Araujo Filho I, Damasceno BP, Egito ES, Silveira IA, Brandao-Neto J, Medeiros AC. Simvastatin improves the healing of infected skin wounds of rats. *Acta Cir Bras* 2007;22(1 Suppl):57–63.
14. Karadeniz Cakmak G, Irkorucu O, Ucan B, Emre A, Bahadir B, Demirtas C, Tascilar O, Karakaya K, Acikgoz S, Kertis G, Ankarali H, Pasaoglu H, Comert M. Simvastatin improves wound strength after intestinal anastomosis in the rat. *J Gastrointest Surg*.2009;13(9):1707–16.
15. Uygur F, Noyan N, Hahaolu A. The effect of simvastatin on the survival of ischaemic skin flap: An experimental study in rats. *J Plast Reconstr Aesthet Surg*. 2009;63(10):1723–32.
16. Holler V, Buard V, Gaugler MH, Guipaud O, Baudelin C, Sache A, Perez Mdel R, Squiban C, Tamarat R, Milliat F, Benderitter M. Pravastatin limits radiation-induced vascular dysfunction in the skin. *Journal of Investigative Dermatology*. 2009;129(5):1280–91.
17. Rajendran NK, Kumar SSD, Houreld NN, Abrahamse H (2018) A review on nanoparticle based treatment for wound healing. *J Drug Deliv Sci Technol*.2018;44: 421-430.

18. Rao M, Mandage Y, Khole I, Munjapara G.Characterization of solid dispersions of simvastatin with PVP K30 and poloxamer 188. *Indian J Pharm Educ Res*.2011;45: 145-152.
19. Alizadeh J, Zeki AA, Mirzaei N, Tewary S, Rezaei Moghadam A, et al. Mevalonate cascade inhibition by simvastatin induces the intrinsic apoptosis pathway via depletion of isoprenoids in tumor cells. *Sci Rep*.2017;7: 1-14.
20. Rohilla A, Rohilla S, Kumar A, Khan MU, Deep A. Pleiotropic effects of statins: A boulevard to cardioprotection. *Arab J Chem*.2016;9: S21-S27.
21. Khoshneviszadeh M, Ashkani-Esfahani S, Namazi MR, Noorafshan A, Geramizadeh B, Miri R. Topical simvastatin enhances tissue regeneration in full-thickness skin wounds in rat models. *Iran J Pharm Res*.2014;13(1):263-9.
22. Rayinda, T., Rizki, I. and Wirohadidjojo, Y. Topical Simvastatin as Treatment of Digital Ulcer in Systemic Scleroderma. In Proceedings of the 23rd Regional Conference of Dermatology (RCD 2018). Portugal: SCITEPRESS; 2021. p465-8.
23. Jia S, Xie P, Hong SJ, Galiano RD, Mustoe TA. Local Application of Statins Significantly Reduced Hypertrophic Scarring in a Rabbit Ear Model. *Plast Reconstr Surg Glob Open*. 2017;5(6):e1294.
24. Jerwood S, Cohen J. Unexpected antimicrobial effect of statins. *J Antimicrob Chemother*.2008;61:362–4.
25. Masadeh M, Mhaidat N, Alzoubi K, Al-Azzam S, Alnasser Z. Antibacterial activity of statins: a comparative study of atorvastatin, simvastatin, and rosuvastatin. *Ann Clin Microbiol Antimicrob*. 2012;11:13.
26. Wang CC, Yang PW, Yang SF, Hsieh KP, Tseng SP, Lin YC. Topical simvastatin promotes healing of Staphylococcus aureus-contaminated cutaneous wounds. *Int Wound J*. 2016;13(6):1150-7.
27. Jun Asai, Hideya Takenaka, Satoshi Hirakawa, Jun-ichi Sakabe, Asami Hagura, Saburo Kishimoto, Kazuichi Maruyama, Kentaro Kajiya, Shigeru Kinoshita, Yoshiki Tokura, Norito Katoh, Topical Simvastatin Accelerates Wound Healing in Diabetes by Enhancing Angiogenesis and Lymphangiogenesis, *The American Journal of Pathology*.2012;181(6):2217-24