Review Article

Usnic acid: A promising bioactive agent for wound healing

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Abstract

Usnic acid is a dibenzofuran derivative found naturally in *P. reticulatum*, a natural lichen. Natural lichen-derived usnic acid is a powerful antibacterial, anti-inflammatory, and antioxidant substance. Due to its capacity to encourage tissue regeneration and lower infection rates, it has attracted considerable attention as a possible bioactive agent for wound healing treatment. Usnic acid has the ability to speed up wound healing, especially in burns, diabetic ulcers, and chronic wounds, according to several in vitro and *in-vivo* investigations. Usnic acid is a topical wound therapy ingredient that can also be used as a wound dressing. However, more research is required to determine its effectiveness and safety in humans as well as the best formulation for uses in wound healing. Usnic acid is typically regarded as harmless when used topically, but when taken orally, some people may have liver damage. It is a promising bioactive agent for the treatment of wounds that has a lot of potential for use in clinical settings in the future. This review discussed the mechanism of usnic acid, formulations and potential future benefits of usnic acid for the treatment of wounds.

Keywords**:** Usnic acid, wound healing, antibacterial, anti-inflammatory, antioxidant, lichens

Introduction

Wound repair is a complex dynamic process integrated sequence of biochemical, cellular and physiological process. The sequential phases of healing process are inflammation, proliferation and migration of connective tissue cells, production of extracellular matrix including collagen synthesis, epithelial cells migration and proliferation leading to neovascularization of wounded tissue. In the inflammatory phase, polymorphonuclear leukocytes and lymphocytes are attracted by soluble mediators and play a key role by secreting cytokines and growth factors. The proliferative phase is characterized by angiogenesis, collagen deposition, epithelialization and wound contraction. The last phase re-modeling phase is characterized by re-model of collagen and other extracellular matrix proteins convert into mature scar tissue (Wilgus, 2008). The effectiveness of wound healing is a dynamic process that is influenced by a number of variables, including age, nutritional status, chronic illnesses, and drug use. However, a number of conditions, including microbial infection, persistent inflammation, and ischemia, can impede or delay the healing process.

Lichens, are symbiotic organisms of fungi and algae, synthesize characteristic secondary compounds. Some species of Parmotrema have also been reported for antimicrobial (Sati and Joshi, 2011; Balaji and Hariharan, 2007) and antioxidant (Sharma and Kalikotay, 2012; Stanly et al., 2011) properties. *Parmotrema reticulatum*, was first described by Taylor (1836; as *Parmelia reticulate* Taylor) based on the reticulated maculae of the upper surface, and characterized by marginal soralia and simple to squarrose rhizines (Divakar et al., 2005). *P. reticulatum* occur in Dima Hasao Hills district of Assam, India. Besides, lichen metabolites exert a wide variety of biological activity including antimycobacterial, antiviral, anti-inflammatory, antiproliferative and cytotoxic effects (Muller, 2001). Usnic acid is a naturally occurring dibenzofuran derivative found in *P. reticulatum*. Usnic acid is a naturally occurring substance that is obtained from lichens and has strong biological

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effects, such as antibacterial, anti-inflammatory, and antioxidant characteristics. This review tries to condense the current body of knowledge regarding the effects of usnic acid on wound healing, which has been the subject of numerous investigations (Chen et al., 2018; de Souza et al., 2019; Sánchez et al., 2018; Santana et al., 2020).

Usnic acid's capacity to damage bacterial membranes and prevent DNA synthesis, which results in bacterial cell death, is what is thought to be responsible for its antibacterial properties. Usnic acid has also been demonstrated to work better together with other antibacterial substances, such as silver nanoparticles, indicating the possibility of using it as a wound dressing (Mendes et al., 2019; Shrestha et al., 2018).

Wound healing and inflammation

Inflammation is a crucial stage of wound healing and is required to start tissue restoration. Yet, persistent inflammation can harm tissues and postpone healing. It has been demonstrated that usnic acid has anti-inflammatory characteristics by preventing the generation of inflammatory cytokines including interleukin-1β and tumour necrosis factor-α. Moreover, usnic acid reduces the activity of cyclooxygenase-2, an enzyme necessary for the production of prostaglandins, which are significant inflammatory mediators. Moreover, research on usnic acid suggests that it can potentially be used as a treatment for inflammatory disorders by reducing the invasion of neutrophils and macrophages in wounded tissues (Li et al., 2018; Maruyama et al., 2000).

Delays in wound healing are frequently caused by oxidative stress, which can also damage tissue by causing protein oxidation, DNA damage, and lipid peroxidation. It has been demonstrated that usnic acid has strong antioxidant activity by scavenging free radicals and preventing lipid peroxidation. Moreover, studies on usnic acid have shown it to boost the activity of antioxidant enzymes like catalase and superoxide dismutase, indicating its potential as a treatment for illnesses linked to oxidative stress (Dal Magro et al., 2013; García-Castillo et al., 2016).

Mechanism of usnic acid in wound healing

In numerous animal models, usnic acid has been demonstrated to facilitate wound healing by accelerating re-epithelialization, angiogenesis, and collagen deposition (Huang et al., 2020). Usnic acid has been found to promote fibroblast migration and proliferation, which are crucial for tissue remodelling and collagen formation. Moreover, usnic acid promotes the production of vascular endothelial growth factor (VEGF), a strong angiogenic factor that is essential for the healing of wounds. Also, it has been demonstrated that usnic acid increases the expression of transforming growth factor-β (TGF-β), a growth factor that encourages the synthesis of extracellular matrix and tissue remodelling (Huang et al., 2020; Maruyama et al., 2000; Huang et al., 2018; Huang et al., 2019).

Usnic acid has been found to have potent antibacterial properties against a variety of harmful microorganisms, such as viruses, fungus, and bacteria. Because of its capacity to damage cell membranes, prevent protein synthesis, and cause oxidative stress, it has been shown to have antibacterial properties (Jasso-Martínez et al., 2018). Usnic acid has been shown to exhibit antibacterial action against both Gram-positive and Gram-negative bacteria, including strains that are resistant to antibiotics, in a number of investigations. Usnic acid has also been discovered to be effective against a number of fungi, including Candida species, and has demonstrated antiviral action against types 1 and 2 of the herpes simplex virus. Usnic acid is a possible option for the creation of novel antimicrobial agents for a variety of applications due to its antibacterial properties. However, more research is required to determine its safety and effectiveness in humans (Shrestha et al., 2018; Li et al., 2018; Huang et al., 2019; Albuquerque et al., 2019;

Table 1. The mechanism behind the pharmacological activities

Pharmacological activities	Mechanism
Anti-inflammatory	Interleukin-1β and tumour necrosis factor production are both inhibited, as is the activity of cyclooxygenase-2, an enzyme necessary for the manufacture of prostaglandins.
Antioxidant	Possess strong antioxidant activity by scavenging free radicals and preventing lipid peroxidation, causing DNA damage, protein oxidation, and lipid peroxidation.
Wound healing	Re-epithelialization, angiogenesis, collagen production, fibroblast migration and proliferation, tissue remodelling, and vascular endothelial growth factor (VEGF), a powerful angiogenic agent, are all expedited.
Antimicrobial	Its capacity to damage cell membranes, stops protein synthesis, and bring on oxidative stress.

Aligiannis et al., 2001).

Various formulations for the management of wounds

For use in topical preparations to promote wound healing, usnic acid has been used in wide variety of formulations. Below are some usnic acids topical formulations that have been reported (Gopikrishnan et al., 2019; Vázquez-Tato et al., 2020):

Hydrogels

According to studies, usnic acid-loaded hydrogels can speed up the healing of wounds in rats by lowering inflammation and boosting the production of collagen (Alves et al., 2021).

A textile-based hydrogel containing Usnic acid was developed for the purpose of wound healing. The dressing has been found to be highly effective in managing wound exudates, providing strength and elongation, and allowing for water vapor permeability. The inclusion of Usnic acid, an active antimicrobial and antibiofilm agent, has resulted in a broad-spectrum antimicrobial activity and antibiofilm property. They were revealed that textile-based hydrogel containing Usnic acid dressing a superior option for the management of wounds, particularly chronic wounds that are infected with biofilm (Thilagavati et al., 2022).

Nanoparticles

Chitosan and alginate were used as a carrier system to create usnic acid nanoparticles. These nanoparticles have demonstrated significant antibacterial action against the major wound infections Staphylococcus aureus and Escherichia coli (Bouarioua et al., 2018).

Polymeric films and membrane

For uses in the treatment of wounds, usnic acid has been added to polymeric films. These films have the potential to release drugs under regulated conditions, and they have also been found to lower the bacterial load in wounds that are infected (Hasani-Sadrabadi et al., 2018).

A membrane containing usnic acid was prepared and its effectiveness for burns healing was evaluated. Usnic acid was first modified into a solid dispersion (SD) system using PVP K-30 in a 1:2 w/w ratio and then formulated into a membrane using poly-vinyl alcohol (PVA), glycerin, and distilled water. The physical and mechanical properties of the membrane were evaluated and it was found to be effective for burn healing activity. The study revealed that a higher concentration of usnic acid solid dispersion in the membrane significantly increased the effectiveness of burn healing. The developed membrane containing usnic acid could be a promising candidate for burns healing and further studies are recommended to explore its potential for clinical use (Lili Fitriani et al., 2021).

The researchers developed collagen-based films containing usnic acid and evaluated their effectiveness as a wound dressing for the healing of dermal burns. Specifically, they used reconstituted bovine type-I collagen to develop a biofilm that incorporated usnic acid. The effectiveness of the biofilm was then assessed by measuring its impact on burn healing in rats. The results of the study showed that the use of the collagen-based films containing usnic acid improved the burn healing process in the rats (Nunes et al., 2011).

Creams

Usnic acid lotions have been shown to accelerate the healing of wounds in rats by lowering swelling and fostering angiogenesis (Andrade et al., 2018).

Sprays

According to research by Santos et al. (2019), usnic acid sprays can speed up the healing of wounds in diabetic rats by lowering inflammation and fostering angiogenesis. To make usnic acid's composition and dosage ideal for use in human wound healing applications, more research is required.

Polymeric scaffold

Developed a functionalized silk fibroin (SF) of usnic acid (UA) and was cutaneous scaffold incorporated with natural medicine usnic acid (UA). The UA has been utilized as an antibacterial and wound-healing reagent, and the UA–SF mixture has been fabricated via electrospinning to produce the UA–SF composite scaffold (USCS). The USCS exhibits improved mechanical properties and stability to protease XIV. The presence of USCS significantly inhibits the growth rate of both Gram-positive and Gram-negative bacteria. They were confirming that USCS can enhance re-epithelialization, vascularization, and collagen deposition in the wound site, thereby promoting the wound-healing process. These findings indicate the potential application of USCS in the treatment of chronic wounds, providing an effective solution for wound management and promoting the healing process (Xiaoying et al., 2021).

Nanogel

Usnic acid (UA) is a dibenzofuran derivative naturally present in lichens, organisms resulting from the symbiosis between a fungus and a cyanobacterium, or an alga. They were reported that UA shows antimicrobial, antitumor, antioxidant, analgesic, anti-inflammatory as well as UV-protective activities (Nicoletta Croce et al., 2022).

A nanogel formulation incorporating usnic acid as an active candidate was developed for targeting oral ulcers, demonstrating low percentages of penetration and permeation. The optimized formulation exhibited the highest release, suitable bioadhesive, particle size and zeta potential values, and was selected for in vivo experiments. The selected usnic acid nanogels showed effective antimicrobial activity against Bacillus Cereus and demonstrated great in vivo wound healing properties. They were found that the optimized usnic acid nanogels have promising therapeutic potential for oral ulcers treatment (Nesrin Coşkunmeriç et al., 2021).

Dressings

Investigated and reported the modern wound dressings have greatly improved the management of different types of wounds, and the choice of wound dressing should be based on the specific characteristics of the wound and the stage of the healing process. Understanding the physiological mechanisms involved in wound healing can also help in the selection and use of appropriate wound dressings (Shi et al., 2020).

The study investigated the effectiveness of topically-applied sodium usnic acid on macroscopic and microscopic changes under dermal injury. The histological results showed that treatment with sodium usnic acid caused a reduction in inflammatory cells and an increase in fibroblast proliferation, granulation tissue, and vascular regeneration. Sodium usnic acid treatment also resulted in earlier complete re-epithelialization, formation of well-organized bands of collagen, and epidermal keratinization. Therefore, the study concluded that the topical use of sodium usnic acid could promote skin wound healing, and this mechanism might be related to anti-inflammatory effects at the wound site (Zhang et al., 2018).

The study investigated the use of new composites for wound dressing prototypes that have improved bactericidal activity. The strategy involved utilizing the synergistic interaction between components to develop more efficient devices. The results showed that the doping effect of usnic acid on undoped polyaniline resulted in important advantages, such as improved bactericidal activity of polyaniline and anti-biofilm properties of the lichen derivative. The resulting material was deposited on polyurethane foam, which enhanced its applicability as a wound dressing. This novel platform was found to be effective against Escherichia coli and Staphylococcus aureus, indicating its potential for clinical use (Marcelo R. dos Santos et al., 2017).

Combination therapy

The present study investigated the potential use of usnic acid, a lichen compound with UV-absorbing properties, as a photoprotective agent in cosmetic products. The study found that the (+)-enantiomer of usnic acid exhibited good photoprotective properties and photostability in a cosmetic formulation, comparable to the commonly used UV filter octocrylene. Furthermore, the combination of (+)-usnic acid with octocrylene in a single formulation resulted in enhanced photoprotection and photostability (Galanty et al., 2021).

The study investigated the dermal wound healing effects of Parmotrema reticulatum lichens, with a possible mechanism involving antioxidant and antibacterial activity. The researchers examined the acetone extract of powdered P. reticulatum lichens for its phytochemical and wound healing properties (Jain et al., 2016). The analysis of the acetone extract confirmed the presence of flavonoids, glycosides, and terpenoids. The researchers concluded that the significant dermal wound healing activity observed may be due to the presence of flavonoids and usnic acid in the acetone extract, which may act through possible antioxidant and antibacterial mechanisms.

Clinical studies

Usnic acid exhibits promise in preclinical study, but further investigation is required to determine whether it will be safe and effective in human clinical trials. Future research may examine the best formulations, doses, and administration methods for usnic acid-based wound healing therapies. Overall, usnic acid shows promise as a therapeutic agent for wound healing; however, more study is required to fully comprehend its mechanisms of action and to create safe and efficient wound care solutions.

Future prospective

The natural compound usnic acid, which is found in lichens, has being studied to determine whether it has any therapeutic advantages, such as the capacity to heal wounds. These are a few potential applications for usnic acid in the treatment of wounds in the future.

Usnic acid can improve wound healing by encouraging cell migration and proliferation, as well as lowering inflammation and oxidative stress, according to studies. The development of topical formulations or wound dressings based on usnic acid in the future may be the main focus. It has been discovered that usnic acid possesses broad-spectrum antibacterial activities, which may be useful in preventing wound infections. Using usnic acid as an antibacterial ingredient in new wound care products may be advantageous.

A common reaction to tissue damage is inflammation, but excessive inflammation can prevent wounds from healing. Usnic acid has been found to have anti-inflammatory properties, which may aid to reduce inflammation and speed up recovery.

To improve wound healing results, usnic acid may be used with other drugs or treatments. For instance, it has been demonstrated to work in concert with honey to speed up wound healing in animal models.

Conclusion

Usnic acid is a naturally occurring substance that possesses potent biological effects, including antibacterial, anti-inflammatory, and antioxidant properties. It has been demonstrated to promote wound healing by enhancing collagen deposition, angiogenesis, and re-epithelialization. In addition, usnic acid increases the activity of antioxidant enzymes and stimulates the expression of growth factors that are involved in tissue repair, among other advantages that are beneficial for wound healing. Furthermore, usnic acid can be incorporated into wound dressings to promote prolonged release and enhance therapeutic efficacy. Although usnic acid has shown potential as a therapeutic agent for wound healing in various animal models, further research is needed to determine its safety and effectiveness in humans. Usnic acid may be utilized as a topical formulation or as a dressing material for wounds to treat burns, diabetic ulcers, and chronic wounds. However, caution should be taken when using usnic acid orally due to the possibility of liver damage. Furthermore, the oral administration of usnic acid is limited, which restricts its therapeutic application. Given its potent antibacterial, anti-inflammatory, and antioxidant properties, usnic acid is a promising bioactive agent for the treatment of wounds.

Conflict of interest: None

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