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Review Article

From past to present, exploring the applications of mupirocin ointment: A comprehensive review

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ABSTRACT

Mupirocin (MUP), a potent antibacterial agent, has been a cornerstone of topical antimicrobial therapy for several decades. As an older, yet widely used antibiotic, MUP has exhibited efficacy against various bacterial strains, making it a versatile tool in the management of a range of infections. The review synthesizes available literature to highlight the evolution of MUP, from its initial discovery to its current status as a go-to topical antibiotic. In the era of rising antibiotic resistance, MUP is positioned as a valuable therapeutic option due to its broad-spectrum activity against gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). Emphasis is placed on its distinctive role in different infections, enhanced efficacy with different additives, and newer drug delivery strategies.

In addition to its classical applications in impetigo and other superficial skin infections, this review delves into emerging indications and novel uses of MUP, potentially expanding its clinical utility. The exploration of combination therapies, alternative formulations, and ongoing research endeavors will contribute to a forward-looking perspective on the role of MUP in future antimicrobial strategies.

1. Introduction

MUP, also known as pseudomonic acid, a drug derived from crotonic acid was first isolated as a secondary metabolite produced by the bacterial stationary phase from Pseudomonas fluorescens in 1971. Since 1976, it has become the first choice of the entire health service provider as a promising antibiotics against Gram-positive bacteria.[1,2]

MUP is one of four structurally related antibiotics, pseudomonic acids A, B, C and D.[3] It has a unique structure with a short fatty-acid side chain linked to monic acid through an ester bond.[4] This allows MUP to inhibit the production of RNA and protein synthesis, thereby preventing the production of isoleucyl-tRNA.[5]

MUP has broad antibacterial coverage against Gram-positive and certain gram-negative bacteria, particularly effective against various Staphylococcus species like *S. aureus*, *S. epidermidis*, *S. pyogenes* (including methicillin-resistant strains), and several Streptococcus species like *S.*

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pyogenes, *S. agalactiae*, and *S. viridans* at concentrations that are achieved with topical application.[2,6,7]

MUP is known globally as the most widely prescribed and used topical antibiotic for the treatment of MRSA, especially in impetigo. In more than 85% of impetigo cases, proper administration of MUP results in the resolution of infectious symptoms. Additionally, MUP effectively eliminates intranasal MRSA colonization in healthcare sites.[8]

Key Highlights

- MUP is effective against Gram-positive bacteria, including MRSA with no cross-resistance to other topically used antibiotics.
- MUP 2% ointment demonstrates high clinical success rates in primary and secondary infections.
- The Infectious Diseases Society of America (IDSA) recommends MUP ointment as the top choice for treating impetigo in infants two months and older, as well as in adults with over 85% effectiveness in removing infectious symptoms.
- MUP exhibits anti-biofilm properties and effectively eliminates MRSA colonization.
- MUP is recommended for surgical site infections (SSI) caused by methicillin-sensitive Staphylococcus aureus (MSSA).
- Its effectiveness in eliminating nasal carriage of S. aureus suggests a potential role in controlling epidemic MRSA in hospitals especially in ICUs.
- MUP resistance is not an issue after short-term intranasal use in surgical or dialysis patients.
- Combining MUP with a biofilm eradicating compound is considered an ideal solution for treating biofilm infections.
- Several new strategies for delivering drugs have been explored to improve patient compliance, reduce resistance, and enhance MUP delivery while overcoming limitations of conventional formulations.

2. Methodology

The report was prepared by searching in scientific resources (Google Scholar, PubMed, Science Direct, Wiley, Scopus, and Springer) using keyword “Mupirocin”. Information was categorized based on various applications and analyzed accordingly. Searches were last updated on June 10, 2024.

3. Unique Mechanism of Action

MUP inhibits isoleucyl transfer RNA, which obstructs bacterial protein and RNA synthesis ultimately leads to cell death. When bacterial isoleucyl transfer RNA is inhibited, it decreases the level of charged transfer RNA in the cell, causing protein and RNA synthesis to cease. This, in turn, causes the death of bacterial cells, especially at high concentrations of MUP. Interestingly, exhibits bacteriostatic activity due to reduced side-chain binding at lower concentrations. MUP minimally affects typical normal skin flora, including Propionibacterium, contributing to the maintenance of skin and natural defense mechanisms.[8] MUP does not develop cross-resistance with other antimicrobial drugs because of its distinct mode of action.[9]

4. Pharmacokinetics

MUP is very slightly absorbed systemically (<1%), and no measurable amounts are seen in the urine or feces after topical treatment.[3] Very high local concentrations of MUP 2% ointment can be obtained by directly applying it to the skin, mucous membranes, or other tissues. Applying MUP ointment followed by an occlusive dressing increases its penetration by 5 to 10 times.[10]

The minimum bactericidal concentration (MBC) of MUP against relevant pathogens is generally 8 to 30-fold higher than the minimum inhibitory concentration (MIC).[11] Topical and transdermal drug delivery systems effectively targets drug action site and maximizing the dose of the drug on the site while minimizing dermal and systemic absorption for locally applied MUP.[12]

5. Effective Bacterial Clearance with 2% Mupirocin Ointment

In recent decades, world have seen a decline in the prevalence of MRSA infection due to a decrease in the use of MUP.[13] In India, high-level MUP-resistant *S. aureus* strains were found in 8.2% of cases, while low-level MUP-resistant strains were present in 17%.[13] Higher prevalence of low-level MUP resistance in *S. aureus* is clinically less significant as MUP ointment containing 20,000 mg/L (2%), can effectively clear such strains.[14]

The widespread utilization of MUP in numerous hospitals has not been implemented, primarily because of concerns about resistance to long-term use and the lack of conclusive evidence. However, studies conducted over a four-year period among surgical patients have failed to demonstrate an increasing trend in MUP resistance, indicating that short-term intranasal administration in surgical or dialysis patients does not present a significant resistance challenge.[15]

In an Indian tertiary healthcare center, coagulase negative Staphylococcus (CoNS) strains showed higher MUP

resistance. Among 100 Staphylococcus isolates, 56 were Staphylococcus aureus, with 87.5% MUP susceptibility and 12.5% resistance.[16]

In another study, 6.75% of Staphylococcus aureus and 19.23% of Coagulase-negative staphylococcus exhibited high-level MUP resistance.[17] This indicates a greater occurrence of MUP resistance among CoNS isolates than among *S. aureus*.

6. Anti-Biofilm Potential of Mupirocin

Biofilms contribute to antibiotic resistance, complicating infection management.[18] A study found that topical MUP via nasal irrigation can decreases *S. aureus* biofilm mass by over 90%. A study suggests a further treatment option for patients with recalcitrant sinusitis could be topical MUP via nasal irrigation, which may help remove *S. aureus* biofilms from the sinus mucosa of patients with chronic rhinosinusitis.[19] The efficacy of a MUP spray containing Eudragit E100 against clinical Escherichia coli isolates was assessed for its anti-biofilm properties, demonstrating substantial anti-biofilm effects at commercial ointments concentrations in wound infections.[20] MUP inhibited the biofilms formation among P. aeruginosa isolates and the production of glycocalyx for 10 days.[21]This highlights the efficacy of MUP in reducing *S. aureus* biofilm mass, coupled with its potent antibiofilm activities against Escherichia coli and P. aeruginosa.

7. Clinical Efficacy of Mupirocin: A Deeper Dive

Skin infections are exceedingly common.[3]Topical antibiotics have been identified as potentially useful in the treatment of traumatic lesions, ecthyma, impetigo, and paronychia.[22]Although there are a lot of more recent topical antibiotics in the market, like Ozenoxacin and Retapamulin, MUP is the antibiotic of choice in actual clinical settings.

7.1. Primary skin infections

MUP 2% ointment has been evaluated against other topical and systemic treatments for a various superficial skin infections.[23] Studies comparing MUP 2% ointment with other treatments, including fusidic acid, found similar clinical and bacteriological efficacy.[24–27] this indicate that MUP plays a useful role in the treatment of superficial skin infections.[28]

7.2. Secondary skin infections

In practice, secondarily infected dermatoses, including infected eczema/atopic dermatitis, and psoriasis, and infected wounds, burns, ulcers and insect bites are a more common therapeutic problem than primary skin infections and *S. aureus* is by far the most common organism involved.[3]

7.3. Impetigo

Topical agents commonly used in the treatment of SSTIs associated with impetigo include MUP.[31] The Infectious Diseases Society of America (IDSA) practice guidelines for the diagnosis & treatment of skin & soft-tissue infections recommend MUP ointment as the topical antibacterial drug of choice in infants two months & older & in adults.[32] Bullous and non-bullous impetigo should be treated with topical MUP twice daily for 5 days.[33]

7.4. Folliculitis

Topical MUP is the first-line agent mainly for Staphylococcal folliculitis.[38] It can be administered to accelerate the healing process of superficial folliculitis indicating that MUP demonstrates a potential for treating such infections.[39]

7.5. Cheilitis

As per American Osteopathic College of dermatology, MUP ointment may be considered for the treatment of cheilitis.[40]

7.6. Nasal vestibulitis (NV)

Intranasal antibiotics (90%, MUP-based), effectively treat mild to moderate NV while severe cases required oral antibiotics. For mild cases, saline humidification, nasal emollients, and use of MUP ointment is recommended.[43]

7.7. Early post tympanostomy/otorrhea

The strategic utilization of MUP ointment emerges as a highly beneficial ototopical intervention against MRSA otorrhea without ototoxicity. Topical MUP appeared to be effective in controlling MRSA tympanostomy tube otorrhea and did not cause local reactions or subsequent hearing loss. Its use for draining ears must be considered “off-label”.[46]

7.8. Nasal decolonization

The American Academy of Orthopaedic Surgeons workgroup and Hospital Infection Society and the British Society for Antimicrobial Chemotherapy recommend preoperative nasal MUP decolonization 3 times daily for at least 5 days for MRSA carriers due to its minimal risk of nasal irritation and low cost.[3,49] MUP has been extensively studied as the most effective decolonizing agent and MUP decolonization contributes to reduced occurrence of clinical cultures positive for *S. aureus* in the intensive care unit (ICU).[50]Centers for Disease Control and Prevention suggests adopting decolonization and pathogen reduction strategies for high-risk patients during high-risk periods. Based on trials, intranasal MUP/iodophor is preferred as the core strategy to decrease carriage of *S. aureus* in ICU and as supplemental strategy for patients hospitalized with

Table 1: Role of MUP in primary skin infections: Insights from clinical trials

Indication	Study Design	Results
Primary skin infections (Superficial Skin Infection)	N= 36 children; MUP vs chlortetracycline[23]	Clinical success rate 95% vs 100%[23]
	N=413; MUP 2% ointment BID vs sodium fusidate TID[27]	Clinical success rate 97% vs 93%[27]
	N= 20; MUP 2% cream bid for 7-14 days[28]	Clinical cure: 95% patients[28]

Table 2: Role of MUP in secondary skin infections: Insights from clinical Trials

Indication	Study Design	Results
Secondary skin infections (eczema, wounds, burns, bites ulcers)	MUP 2% ointment vs polyethylene glycol vehicle[3]	Bacterial eradication rate: (MUP vs vehicle) 90% vs 53%; Overall eradication rate (*S. aureus*) 94% vs 40%[3]
Infected dermatoses (atopic dermatitis, eczema, seborrheic, dermatitis, or contact dermatitis neurodermatitis)	N=92; MUP 2% ointment vs polyethylene glycol vehicle; TID ; 7-9 days[29]	All pathogen: Marked or Moderate improvement (79% MUP vs 65% Vehicle) S.aureus/S.pyogenes: Marked or Moderate improvement (85% MUP vs 53% Vehicle).[29]
Secondarily Infected Eczema	N=40; MUP with Steroid[30]	Effectively eliminates S.aureus from the infected eczema and from the anterior nares.[30]
Atopic Dermatitis	MUP 2% ointment; BD (7days)[3]	Reduced mean number of S.aureus colony forming units/cm^{2}from 33,250 to 20.[3]
	MUP 2% ointment; BD (14 days)[3]	Good resolution of clinical features. Loss of Itch in 8 patients within 24 hours.[3]
Infected Burns	N=17 children (Multi-resistant S.aureus, did not respond to povidone iodine or Mafenide acetate); MUP 2%; BD (5 days)[3]	Clinical and bacteriological success rates : 96%.[3]
	N=8 patients; failed to respond to silver sulphadiazine, povidone iodine, or chlorhexidine; MUP 2% (5 to 9 days).[3]	*S. aureus* (11 wounds) and *S. pyogenes* (2 wounds) were eliminated within 7 days.[3]

Table 3: Role of MUP in impetigo: Insights from clinical trials

Indication	Study Design	Results
	N=28 (mild to severe impetigo); MUP.[34]	Clinical cure 86%.[34]
	Adults with impetigo infection treatment with MUP.[3]	98% overall improvement.[3]
Impetigo	N=102 MUP 2% ointment vs vehicle ointment base TID for up to 12 days.[35]	Clinical and Bacteriological Cure (%): 68% vs 54%.[35]
	N=33; uncomplicated impetigo; MUP 2% ointment vs neomycin 1% ointment BID (7- 14 days)[36]	Clinical cure rate: 100% vs 76.5%.[36]
	MUP 2% ointment (n=5) vs fusidic acid 2% ointment (n=8); TID (7 days); impetigo.[37]	Similar clinical improvement Treatment failure: Fusidic acid.[37]

Table 4: Role of MUP in folliculitis: Insights from clinical trial and case studies

Indication	Study Design	Results
Folliculitis	N=46; pyogenic skin infections; MUP tid for 5 days[40]	Authors rated 43 of the 46 patients as clearing completely after treatment with MUP.[40]
	N=1; folliculitis decalvans; Rifampicin 600 mg OD + topical 2% MUP ointment BID (10 weeks)[41]	Pain and folliculitis disappeared, and no new pustules formed.[41]

Table 5: Role of MUP in cheilitis: Insights from case reports

Indication	Study Design	Results
Cheilitis	N=1; Candidal cheilitis/exfoliative cheilitis; MUP 2% ointment (14 days) + Tacrolimus 0.1% ointment + petroleum jelly.[42]	Improved symptoms of scaling, crust and xerosis of upper and lower lips.[42]
	N=1; Exfoliative cheilitis; Excimer laser therapy + MUP ointment (30 days) + Doxycycline 100 mg daily.[42]	Improved symptoms of xerosis.[42]

Table 6: Role of MUP in nasal vestibulitis: Insights from case reports

Indication	Study Design	Results
Nasal Vestibulitis	N=1; swelling at the nasal vestibulum, erythema, and edema; intranasal topical MUP and oral sodium fusidate 7 days.[44]	Complete resolution of symptoms within 7 days.[44]
	N=1; recurrent exquisitely tender unilateral erythema and edema of the nasal tip;topical MUP (BID, 3 days).[45]	Complete resolution of nasal pain, skin redness, and swelling within 1 week.[45]

Table 7: Role of MUP in posttympanostomy/ Otorrhea: Insights from clinical studies

Indication	Study Design	Results
Tympanostomy	N= 67; tympanostomy tube coated with topical MUP.[47]	Low incidence of post-tympanostomy tube otorrhea.[47]
Otorrhea	Topical MUP ointment (n=16) vs ofloxacin drops (n=10).[48]	Complete elimination of MRSA in the MUP group (100%) vs ofloxacin group (20%).[48]

Table 8: Role of MUP in nasal decolonization: Insights from clinical studies

Indication	Study Design	Results
Nasal Decolonization	N=44; Nasal carriers of *S. aureus*; lanolin base, with or without MUP 2%, (QID; 5 days).[3]	Clearance of bacteria in MUP group within 48 hours, whereas the lanolin base had no effect on bacterial growth.[3]
	N=4000; MUP vs placebo.[52]	MUP Nasal decolonisation rates MUP: 83.4% vs Placebo: 27.4%.[52]
	MUP vs Neomycin; Peritoneal dialysis.[53]	Decolonization rate MUP: 100% vs Neomycin: 40%.[53]
	MUP vs Iodophor for universal ICU nasal decolonization with Chlorhexidine gluconate bathing.[54]	Nasal iodophor inferior to nasal MUP to prevent MRSA infections and all-cause bloodstream infection in ICU.[54]

midline catheters or central venous catheter outside the ICU. However, findings indicated that nasal iodophor was less effective than nasal MUP.[51]

7.9. Intraocular surgery

Using MUP nasal ointment before intravitreal injections or intraocular surgery is a novel approach to lower the rates of conjunctival contamination.[55] Pathogens that cause postoperative endophthalmitis are more likely to colonize elderly people, men, patients with lacrimal duct obstruction, and immunocompromised patients.[56] Administration of MUP nasal ointment for 3 days before intraocular surgery led to a reduction in nasal and conjunctival flora (with or without 5 % povidone-iodine preparation), aligning with the results observed with 5-day prophylactic use.[57]

7.10. Surgical site infection

Preoperative administration of intranasal MUP is beneficial for patients undergoing cardiac and orthopedic surgery, as cardiac surgery has a high SSI risk of up to 33%, and orthopedic procedures may require implant removal. WHO Guidelines Development Group conducted meta-analysis found that nasal decolonization using MUP ointment, with or without chlorhexidine gluconate soap body wash, significantly reduced the incidence of SSI in patients with known *S. aureus* carriage compared with placebo or no treatment.[58]

The European Association of Cardio-Thoracic Surgery (EACTS) 2017 guidelines suggest intranasal application of MUP twice daily is advised for four days before the procedure for elective patients undergoing cardiac surgery. On the other hand, the 2019 guidelines from the Enhanced Recovery after Surgery Society recommend universal decolonization using MUP for perioperative care in cardiac surgery. Additionally, an expert consensus review published in the Journal of Thoracic and Cardiovascular Surgery regarding the prevention and management of sternal wound infection suggests routine administration of MUP in all cardiac surgery cases in the absence of positive PCR testing or nasal cultures for *S. aureus*.[59]

National Institute for Clinical Excellence (NICE) guidelines in the UK advise considering MUP whenever MSSA is suspected cause of SSI.[60]

7.11. Infected ulcerated skin lesions

Topical antibiotics such as MUP is widely used for superficial skin ulceration with inflammation.[61]

7.12. Peri-prosthetic joint infection (PJI)

There is strong evidence that nasal *S. aureus* decolonization is effective at reducing PJIs with intranasal MUP ointment being sole treatment with high quality evidence.[62]

7.13. Hemodialysis central venous catheter exit sites

Decolonization with MUP offers protection against *S. aureus* infections in dialysis patients.[64] Recent evidence indicates a notable decrease in catheter-associated infection rates through consistent topical application of MUP to the exit sites of non-cuffed, non-tunnelled hemodialysis cannulae.[65]

7.14. Zoon's balanitis

Although circumcision is the gold standard therapy, topical calcineurin inhibitors have recently been efficacious. The excellent safety profile of MUP may lead clinicians to consider it as first-line topical therapy in patients with newly diagnosed zoon balanitis.[67]

8. Mupirocin Ointment in Clinical Practice: Special Population Considerations

MUP is FDA-approved for pediatric populations from 2 months of age and older.[8] A 12-hour-old neonate with transient neonatal pustular melanosis treated with topical MUP solely for prophylaxis against secondary bacterial infection. The lesions resolved within four days, with only hyperpigmented macules visible in areas.[69]

Low-dose MUP in pregnancy shows no teratogenicity in limited studies. It is preferred topical option for both pregnant and lactating women.[70] For pregnant women with atopic dermatitis, MUP is preferred due to its reduced allergenicity compared to neomycin and bacitracin and superior efficacy against both MSSA and MRSA.[71] While systemic renal excretion necessitates caution for MUP in severe renal impairment, topical application at the catheter site significantly reduces *S. aureus* colonization and peritonitis and exit site infection risk to a considerable amount in patient with chronic kidney disease.[8,72,73]

MUP is considered as an empiric antibiotic by experts in treatment of end stage liver disease complicated by skin or soft tissue (non-suppurative- cellulitis/erysipelas) infections.[74]

9. Improved Efficacy of Mupirocin With Added Actives

Combining MUP with a biofilm eradicating compound is an ideal solution for treating biofilm infections.[75] Combining MUP with 1,8-cineole effectively eradicated MRSA isolates growing in biofilm.[76] The combination of MUP and Cinnamon Oil (CO) at concentrations ranging from 0.2 μg/ml to 5.218 mg/ml showed better synergistic antibiofilm effect against sessile *S. aureus*. These formulations substantially enhanced their capacity to eradicate biofilms, thereby increasing efficacy.[75]

HT61, a cationic bactericidal agent derived from quinolone, exhibits efficacy against both MRSA and MSSA isolates and synergizes with MUP against *S.*

Table 9: Role of MUP in infected ulcerated skin lesions

Indication	Study Design	Results
Infected ulcerated skin lesions	N=8; chronic leg ulcers; MUP 2% ointment OD (13 to 22 days).[3]	Improvement: 75% of patient.[3]
	MUP 2% ointment BD; pretreatment evidence of S. aureus and/or β-haemolytic streptococcus infection.[3]	Clinical improvement (episodes of ulceration) 73.33%. Symptoms (pain, itching, weeping, pus formation, crusting, sloughing, inflammation, and dermatitis) significantly reduced in 68% of patients.[3]
	N=48; MUP 2% ointment vs Vehicle (TID, 5-10 days).[3]	Clinical response rate: 96% vs 67%.[3]

Table 10: Role of MUP in Periprosthetic joint infection

Indication	Study Design	Results
Periprosthetic joint infection	MUP 2% vs Placebo[63]	MUP nasal decolonisation reduced PJI compared to control groups.[63]
	MUP vs Neomycin vs Octenidine[62]	MUP (89.1%) and neomycin (90.9%) more effective at decolonisation than octenidine.[62]

Table 11: Role of MUP in Hemodialysis central venous catheter exit sites

Indication	Study Design	Results
Hemodialysis central venous catheter exit sites	2% calcium MUP ointment TID a week.[65]	Safe and substantially reduced the risk of catheter-related infections and premature catheter removal.[65]
	Chronic renal failure patients with non-cuffed, non-tunnelled haemodialysis catheters treated with MUP.[66]	Topical MUP prophylaxis reduced *S. aureus* bacteraemia rates from 8.9 to 0.7 episodes per 1000 patient-days.[66]

Table 12: Role of MUP in Zoon's Balanitis

Indication	Study Design	Results
Zoon's Balanitis	MUP 2% ointment[68]	Lesion's clearance within 6 weeks of use.[68]
	MUP 2% ointment[67]	Complete response to MUP monotherapy.[67]

aureus isolates.[77] HT61 and MUP exhibited significant antibacterial activity and could effectively combat bacterial infections in vivo.[78]

Propolis possess antibacterial properties with both bacteriostatic and bactericidal activities.[12] Additionally, when combined with MUP, propolis showed promise in reducing bacterial cell counts and mitigating inflammatory responses in an in vivo model, indicating potential as a treatment option against MRSA infections.[79]

D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) modified MUP and silver complex (TPGS/Mup-Ag) offers advantages like small particle size and better bacterial internalization. Released silver ions from Mup-Ag show synergistic antibacterial effects with MUP confirmed in vivo to inhibit skin infection progression, accelerate wound healing, and reduce systemic inflammation, offering a promising strategy against MuRSA and MUP resistance.[80]

Micronized alaptide significantly enhanced the permeation of MUP through the skin within the first hour after administration, showing an approximately 5-fold increase in permeation compared to the control. This suggests that micronized alaptide may have the potential to improve transdermal delivery of MUP. Combination of alaptide with MUP can alter the depth and velocity of MUP's permeation into and through the skin.[81]

10. Recent Advances in Mupirocin Delivery Strategies

MUP has certain restrictions, such as a high protein binding, short half-life and drug resistance. To address these challenges, controlled use, decolonization targeting, and a 10-day treatment duration without repeating for 30 days are recommended. Consequently, various innovative drug delivery methods have been explored to overcome the

limitations of conventional formulations, enhance patient compliance, decrease resistance and improve MUP delivery.

Novel drug delivery system of MUP to overcome its limitations, includes microsponges, nano-emulsions, liposomes, microsphere-based scaffolds, nanocapsules, nanofibers, nanostructured lipid carriers, patches, and hydrogels, for treating wound infections. MUP carried in nanocarriers decreased MIC and improved wound healing. MUP scaffolds had higher water absorption, provided prolonged release, showed strong tensile strength, reduced dressing changes, and enhanced antimicrobial activity. Microsponges sustained drug release, focusing on lowering dosing frequency, and had about 5 times better retention on rat skin compared to MUP ointment.[82,83]

Hydrogels loaded with MUP and granulocyte-macrophage colony-stimulating factor (GM-CSF) accelerates diabetic wound closure, offering a promising treatment option.[84]

MUP-loaded PEGylated nanoliposomes and liposomal hydrogels showed promise for systemic drug delivery and effective treatment of burn infections, respectively.[82] The sustained release ability of liposomes in the formulation allowed for less frequent administration, enhancing patient comfort and minimizing stress and pain associated with burn care compared to traditional daily applications.[82]

Microcapsules formulated with Eudragit RS 100 polymer enabled local delivery of MUP, enhancing therapeutic efficacy and skin retention. Drug-loaded micro particles effectively maintained their performance even after 10 months of storage. This indicated the stability of the formulation and demonstrated its potential for long-term use. It may necessitate adjustments in the initial dosing regimen, possibly shifting toward once-a-day formulations to optimize the therapeutic benefit.[82]

MUP-loaded nanoemulsions with essential oils showed superior MUP deposition in the skin, indicating potential for acute or prophylactic management of skin infections.[85]

Breakable foam formulation exhibited an antimicrobial effect against *S. aureus* which was 0.75-fold better. Its unique property of collapsing upon slight tap is highly beneficial for application with medical gauze. Additionally, it has quick collapse time, excellent spreadability and superior antibacterial efficacy which can be explored for burn wounds with a minimum touch. Studies in subjects with psoriasis and eczema indicates that the foam delivery system is easy to use, provides a cooling or emollient effect, increases patient acceptance, and is quickly absorbed than traditional topical dosage forms.[83]

11. Novel Mechanisms of Mupirocin

11.1. For promoting wound healing

A latest study explored the potential of MUP beyond its antibacterial properties in wound healing. It was the first to investigate MUP's impact on human keratinocytes, revealing its ability to stimulate their proliferation and increase the production of various growth factors. Additionally, previous research indicates MUP's role in enhancing TNF-α production by macrophage during the initial inflammatory phase of wound healing. Overall, these findings indicates that MUP may play a significant role in promoting wound healing through multiple mechanism beyond its antimicrobial effects.[86]

11.2. In treating psoriasis like dermatitis

MUP is not a standard treatment for psoriasis; it can be considered in cases of bacterial colonization. Recent preclinical research has revealed a potential link between MUP and psoriasis treatment, shedding light on its mechanism of action.

Key findings indicate that psoriatic skin has elevated expression of isoleucyl-tRNA synthetase (IARS), a target of MUP. In an imiquimod (IMQ) -induced psoriasis mouse model, MUP reversed keratinocyte proliferation, suppressed inflammatory cytokine expression, and reduced immune cell infiltration. Moreover, MUP inhibited proliferation and promoted apoptosis in cultured human keratinocytes.

A significant discovery indicates that preventing immune cells infiltration by inhibiting IARS may be one mechanisms by which MUP exerts its effect in psoriasis. Overall, while MUP is not traditionally used to treat psoriasis, this research indicates its potential as a novel therapeutic approach for this complex skin condition.[87]

12. Approved Indications, Dosage and Administration

The USFDA (December 1987) approved MUP 2% ointment for the topical treatment of impetigo caused by susceptible isolates of *S. aureus* and *S. pyogenes*.[88]

MUP 2% ointment has been approved in Europe (March 1985) for skin infections, e.g. impetigo, folliculitis, furunculosis due to *S. aureus*, including methicillin-resistant strains, other staphylococci, streptococci & Gram-negative organisms such as E. coli and Haemophilus influenza.[89]

The Indian Regulatory Authority [CDSCO/DCGI-September 1991], approved MUP 2% w/w ointment for bacterial skin infections.[90]

MUP ointment is indicated for the topical treatment of impetigo due to susceptible isolates of *S. aureus* and *S. pyogenes*.[31] The dosage and administration of MUP ointment 2% can vary depending on the specific condition. Patients should apply a small amount of MUP ointment thrice daily to the affected area with the option to cover the treated area with gauze if preferred. Patients who do not show a clinical response within 3-5 days should be re-evaluated.

Expert Opinion

Topical MUP a potent antibiotic, has versatile utility and recognition for its multifaceted applications in clinical settings. In India, MUP is the first choice of clinicians for the treatment of MRSA causing severe infections viz., skin and soft tissue infection. From impetigo to minor wound infections, MUP demonstrates consistent efficacy, often surpassing alternative topical antibiotics. MUP shows promising results in neonatal acne. It is preferred in pregnant and lactating women, and patients with chronic kidney disease due to its safety profile and efficacy. Experts consider it a valuable option for empiric treatment of skin infections in end-stage liver disease. MUP should be applied to the patient's nares for three days in a row, if a preoperative nasal culture is positive for MRSA. This will decrease the patient's likelihood of carrying MRSA at the time of surgery and lowers the risk of operative infections. MUP is commonly used in wound care for both acute and chronic wounds, it is often utilized as strategy to help stop the spread or limit recurrent bacterial infections. Among 176 non-duplicate MRSA strains from 30 Indian hospitals, the majority (78.41%) exhibited sensitivity to MUP. Despite the presence of resistance in India, the majority of MRSA strains exhibit sensitivity to MUP, with only a small percentage showing high or low-level resistance. Emphasizing rational usage and not recommending for use longer than two weeks can help maintain this favorable trend. Furthermore, regulating the over-the-counter sale and preventing the indiscriminate use of MUP are essential steps toward preserving its effectiveness.

13. Conclusion

MUP has been widely prescribed because it is currently the best topical antibiotic for gram-positive bacteria currently available. Off-label use and continuing research are examining new applications of MUP, including its possible efficacy against deep infections and non-typical bacteria, in addition to its approved topical administration for skin infections. MUP is a relatively potent decolonizing agent and is effective in managing otorrhea, serving as an additive in sinonasal irrigation, and acts as prophylaxis to prevent peritoneal dialysis catheter site infection. It has been proven to be more effective than iodophor in reducing intranasal *S. aureus* levels and theoretically lowering biofilm formation. MUP is considered a core management strategy to reduce the carriage of *S. aureus* in all patients admitted to the ICUs. Furthermore, MUP has been used to promote the wound healing process which is associated with increased keratinocyte proliferation. The therapeutic efficacy of MUP can be enhanced by combining it with other agents and using a suitable biocompatible carrier that promotes and supports cell viability and cell proliferation together, with sustained release of MUP.

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15. Conflict of Interest

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