International Journal of Research in Medical Sciences
Talathi A et al. Int J Res Med Sci. 2023 Sep;11(9):3376-3386
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20232796

Original Research Article

Efficacy and safety of SilverNova™ skin cream as adjuvant to oral and topical antifungals in treatment of fungal skin infections

Abhay Talathi[1], Avinash Jadhav[2], Sanjay Purohit[3], Anirudh Mehta[4]*

[1]Skin Space Clinic, Mumbai, Maharashtra, India
[2]Jyoti Multispecialty Clinic, Pune, Maharashtra, India
[3]Maven's Hospital, Ajmer, Rajasthan, India
[4]Viridis BioPharma Pvt. Ltd. Mumbai, Maharashtra, India

Received: 22 July 2023
Revised: 11 August 2023
Accepted: 19 August 2023

***Correspondence:**
Anirudh Mehta,
E-mail: adme@viridisbiopharma.com

ABSTRACT

Background: To evaluate the efficacy and safety of SilverNova™ skin cream, composed of SilverSol® (a patented colloidal nano silver technology from American Biotech Labs, USA) with other skin rejuvenators (coconut oil, vitamin E, and hyaluronic acid), as an adjuvant to topical and oral antifungals in the treatment of fungal skin infections like tinea and intertrigo.
Methods: This prospective clinical study enrolled 80 patients with tinea corporis, tinea cruris, tinea manus, tinea pedis infections, and intertrigo. The patients were randomized to receive either SilverNova™ skin cream and clotrimazole cream (n=40) or clotrimazole cream (n=40) alone applied topically as an adjuvant to oral antifungal therapy for 14 days. The primary endpoints were the reduction of clinical signs and symptoms of the infection at the end of the treatment and the proportion of patients with therapeutic cures.
Results: SilverNova™ skin cream exhibited better efficacy and safety than clotrimazole cream, though without reaching clinical significance at the end of the treatment. On the 14th day, there was an improvement in clinical signs and symptoms of fissuring/cracking, erythema, maceration, scaling, pruritus, and burning/stinging from baseline in patients with tinea infections, and intertrigo in both the treatment groups. A higher proportion of patients reported therapeutic cures at the end of the treatment, numerically better with SilverNova™ skin cream group. No drug-related adverse events occurred.
Conclusions: SilverNova™ skin cream is effective and well tolerated as an adjuvant to topical and oral antifungals for the treatment of fungal skin infections like tinea and intertrigo.

Keywords: AgNPs, SilverSol® technology, Dermatophyte, Intertrigo, Seborrheic dermatitis, Silver nanoparticles, Tinea infections

INTRODUCTION

Fungal skin infections are a common global problem. These infections have a diverse spectrum of the extent and severity of the infection and the features of the infecting fungi.[1] Tinea infections, cutaneous candidiasis, Candia intertrigo, and seborrheic dermatitis are the most common fungal skin infections.[2] Three genera of dermatophytes are the etiological agents responsible for tinea infections, including *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton* spp. These dermatophytes infect nonviable, keratinized cutaneous structures like stratum corneum, nails, and hair.[2,3] Tinea infections are named according to the anatomic site of infection. Tinea corporis, known as ringworm of the body, is a dermatophytic infection on the skin of sites other than the face, hands, feet, or groin. Tinea cruris, also termed 'jock itch,' occurs in the groin fold. Tinea

pedis, also called 'athlete's foot,' is the most common dermatophyte foot infection. Similarly, a tinea infection of the scalp is called tinea capitis, and that of the hand is called tinea manuum.[4]

Cutaneous candidiasis is another common fungal infection that most frequently affects intertriginous or occluded areas, mucous membranes, glabrous skin, and nails.[3] Local skin conditions such as increased humidity, occlusion, broken skin barrier, and altered microbial flora are often *responsible for* cutaneous *Candida* infections. A variety of *Candida* species are responsible for cutaneous candidiasis, of which *C. albicans* is the most common causative pathogen in human infections.[5]

Intertrigo, also termed intertriginous dermatitis, is a superficial inflammatory dermatitis occurring on two closely opposed skin surfaces due to moisture, friction, and lack of ventilation.[6] Intertrigo is most commonly found in the groin, axillae, and inframammary folds.[7] It can also affect other areas of the body, including antecubital fossae; umbilical, perineal, or interdigital areas; neck creases; and folds of the eyelids.[8] Skin inflammation in intertrigo is often exacerbated by bodily secretions, including sweat, urine, and feces.[7] Various fungi, including yeasts, molds, and dermatophytes, also exacerbate intertrigo. *Candida* is the most commonly associated fungus with intertrigo. Dermatophytes, including, *T. rubrum* and *T. mentagrophytes*, may also worsen interdigital intertrigo.[4]

Seborrheic dermatitis is a recurrent, chronic inflammatory skin condition that affects areas rich in sebaceous glands, such as the scalp, face, chest, and intertriginous areas. Dandruff is considered a mild or initial form of seborrheic dermatitis. Seborrheic dermatitis is most likely due to infection caused by *Malassezia* fungus species.[9]

Fungal infections of hair, nail, and skin are widespread in India. A cross-sectional study by Lakshmanan et al found a 27.6% prevalence of superficial fungal infections among 297 patients included in the study. Dermatophytosis prevalence was 75.6%, while non-dermatophytosis was 24.4%. *T. rubrum* was the primary dermatophyte (79%), and Candida (60%) the top non-dermatophyte. Recent years show an epidemiological shift in Indian dermatophytes. *T. rubrum* remains common but less prevalent. *T. mentagrophytes* has emerged as a significant isolate with increased prevalence compared to the past.[11] A recent multicentric Indian study by Tahiliani et al revealed tinea corporis as the predominant dermatophytosis type (71.4%), followed by tinea cruris (62%). In their study, *T. rubrum* led as the most identified dermatophyte (68.4%), followed by *T. mentagrophytes* (29.3%). Interestingly, *T. mentagrophytes* prevalent in humid cities, while *T. rubrum* prevalent in noncoastal regions.[12]

Antifungal resistance and skin barrier defects are mainly responsible for chronic Tinea infections and relapse. Despite existing topical and oral antifungals, high fungal infection rates persist due to resistant strains and treatment non-compliance owing to their toxicity.[13,14] On the other hand, skin barrier function defects, including increased TEWL (Trans Epidermal Water Loss) and decreased stratum corneum hydration, reduce the cure rates and significantly increases relapse rates among those who initially achieved a cure.[15] There is a need to develop a newer antifungal therapy to overcome the limitations of current antifungal therapies.

Inflammation can complicate tinea infections with pronounced erythema, swelling, pruritus, and burning. Scratching due to itching often leads to secondary bacterial superinfections in response to pruritus and abrasion of the skin, contributing to recalcitrant and chronic infections. This highlights the need for a treatment addressing both fungi and bacteria in mixed infections, while also providing anti-inflammatory effects.[16-18]

Indian association of dermatologists, venereologists, and leprologists (IADVL) Task force against recalcitrant tinea (ITART) highlights that a concomitant or adjuvant application of skin barrier repair formulations are of great value in both treatment and preventing recurrences of dermatophytosis.[19]

Nano-particles are an innovative approach to delivering newer therapies to the site of action. There has been a growing interest in silver nano-particles (AgNP), also called colloidal nano silver, over the years due to their potential application in treating skin infections.[20] Antifungal and anti-inflammatory properties of AgNPs are of special interest in the management of fungal skin infections.[13,21] Ample evidence supports silver nanoparticles for treating fungal skin infections. Applying them alongside standard care can improve outcomes. This study assessed SilverNova™ cream with SilverSol® (patented colloidal nano silver technology from American Biotech Labs, USA) and skin-revitalizing agents like coconut oil, vitamin E, and hyaluronic acid as an adjuvant to oral antifungals for fungal skin infections. SilverNova™ is a trademark of Viridis BioPharma Pvt. Ltd., Mumbai.

METHODS

Patients

Male and female patients above 18 years were enrolled in the study. The key inclusion criteria were the presence of any one skin infection caused by *T. rubrum*, *T. mentagrophytes*, *Microsporum canis*, and *Epidermophyton floccosum*, which included tinea corporis, tinea cruris, tinea manus, and tinea pedis infections. Patients with intertrigo were also eligible to get enrolled in this study. Signs considered for scoring were fissuring/cracking, erythema, maceration, and

scaling, and symptoms were pruritus and burning/stinging. Patients were required to have the sum of clinical signs and symptoms scores of the target lesion of at least four. In addition, the target lesions must have a minimum score of two for erythema and a minimum score of two for either pruritus or scaling.

Patients with a history of current psoriasis, lichen planus, or contact dermatitis involving the feet within the previous 12 months were excluded from the study. Other key exclusion criteria were current uncontrolled diabetes, confluent, diffuse moccasin-type tinea pedis of the entire plantar surface, use of antipruritics, including antihistamines, within 72 hours, use of topical corticosteroids, topical antibiotics or topical antifungal therapy (e.g., clotrimazole, econazole, fluconazole) within two weeks, use of oral terbinafine or itraconazole within two months, etc. Female subjects who were pregnant, breastfeeding, or planning a pregnancy were excluded from the study.

Study design and oversight

This was a prospective, interventional, randomized, parallel, double-blind, active-controlled clinical study. The study was conducted at two clinical settings, Jyoti multispecialty clinic, Pune, and Maven's hospital, Ajmer. The study was conducted from 14th September 2022 to 18th October 2022. The study was approved by the appropriate Institutional and Independent Ethics Committees and was registered in clinical trials registry-India (CTRI registration no: CTRI/2022/06/043512 Dated: 27/06/2022). The trial was conducted as per the ICMR Guidelines (2017) for biomedical research on human subjects, ICH GCP (E6R2) guidelines, new drug and clinical trials rule 2019, Declaration of Helsinki (Brazil, 2013) and in accordance with other applicable guidelines. All patients provided written consent to participate in the study prior to being screened. The investigator explained the details of the study procedure to each patient during the screening visit.

A total of 80 patients were enrolled in the study and were randomized to receive either SilverNova™ skin cream and clotrimazole (topical antifungal) cream (test product; n=40) or only clotrimazole (topical antifungal) cream (reference product; n=40) as per study design in Figure 1 below. Each group included 20 patients with tinea skin infection (tinea corporis, tinea cruris, tinea manus, tinea pedis infections, and seborrheic dermatitis infection) and 20 patients with intertrigo. The total duration of the study was 21 days, with 14 days of treatment and follow- up on day 21.

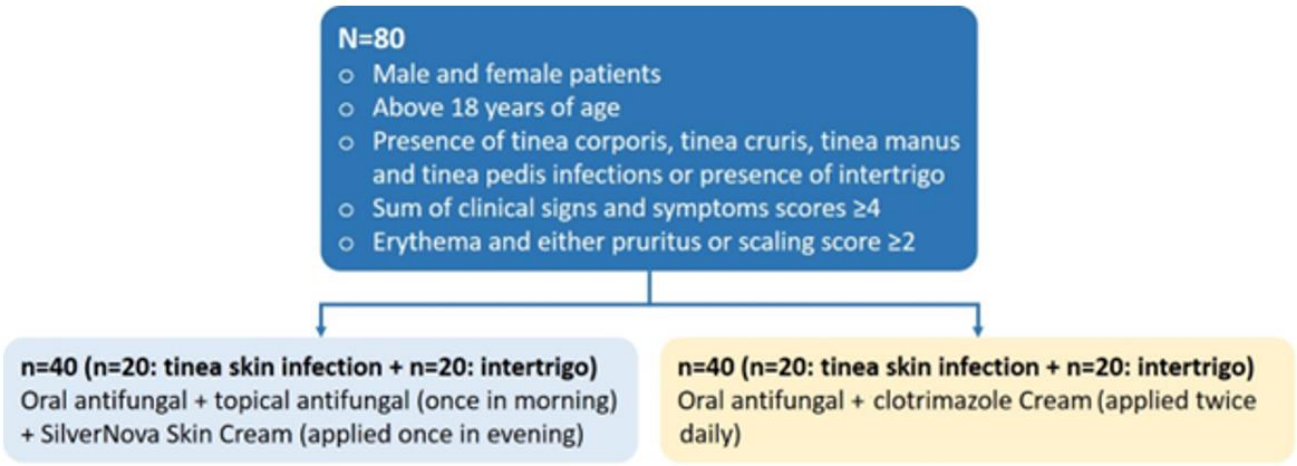

Figure 1: Study design.

On day one first visit was planned to assess the baseline parameters. On day 7±3 second visit was planned. The third visit was scheduled on day 14, i.e., at the end of the treatment (EOT), and a follow-up visit was planned for day 21.

Treatment

Patients in the test group received an oral antifungal, a topical antifungal once in the morning, and SilverNova™ skin cream applied once in the evening. Patients in the reference group received topical antifungal (Clotrimazole cream) twice daily along with standard care treatment of oral antifungals as in the test group. A thin film of test and reference cream were applied to the affected areas of the skin. One fingertip unit (a line from the tip of an adult index finger to the first crease) was enough to cover an area twice the size of an adult hand.

Primary and secondary endpoints

The primary endpoints evaluated were reduction of clinical signs and symptoms assessed by clinical examination for fissuring/cracking, erythema, maceration, scaling, pruritus, and burning/stinging from baseline to EOT on day 14 for tinea skin infection and intertrigo [0=none (complete absence of any sign or symptom), 1=mild (slight), 2= moderate (definitely present), 3=severe (marked, intense)] and proportion of patients in each group with a therapeutic cure for fissuring/cracking, erythema, maceration, scaling, pruritus, burning/stinging from baseline to EOT on day 14 for tinea skin infection and intertrigo. A therapeutic cure was defined as having no signs and symptoms of tinea skin infection and intertrigo.

The secondary endpoint was self-assessed general health from baseline to EOT on day 14. Adverse events were monitored for assessment of safety. Clear photographs of lesions were taken at baseline and EOT on day 14.

Statistical analysis

The data were analyzed with a 5% significance level and 80% power for study using SAS. The difference within the group was assessed using the appropriate statistical parametric and non-parametric tests. A separate analysis was performed for primary and secondary endpoints.

RESULTS

Demographics and other baseline characteristics

All 80 patients completed the study. All the patients were compliant during the treatment and were considered for statistical analysis. The baseline characteristics of the patients are given in Table 1.

Primary endpoints

Reduction of clinical signs and symptoms

After 14 days of treatment with SilverNova™ skin cream and clotrimazole cream, there was a reduction in clinical signs and symptoms of fissuring/cracking, erythema, maceration, scaling, pruritus, and burning/stinging from baseline in patients with tinea infections shown in the Table 2.

At the end of the study, patients showed either none or mild signs and symptoms of tinea infections in both treatment groups. However, higher improvement was seen in the SilverNova™ skin cream and clotrimazole cream group as compared to the clotrimazole cream group.

Similar results were reported in patients with intertrigo. There was a reduction in clinical signs and symptoms of fissuring/ cracking, erythema, maceration, scaling, pruritus, and burning or the stinging from baseline to EOT following the treatment with SilverNova™ skin cream and clotrimazole cream shown in the Table 3. There was no difference between the treatment groups. At the end of the treatment, patients in both groups showed either none or mild signs and symptoms of intertrigo. Although not statistically significant, a higher proportion of the patients in the SilverNova™ skin cream group showed improvement in signs and symptoms of skin infection and the intertrigo than clotrimazole cream at EOT.

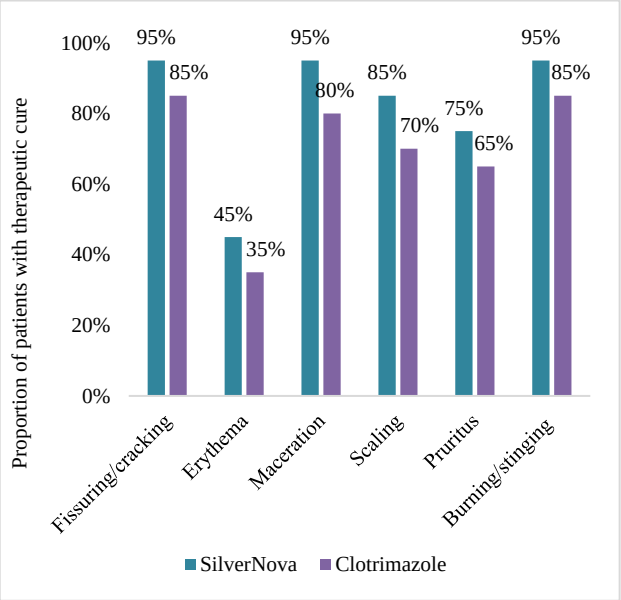

Figure 2: Proportion of patients with tinea infections with therapeutic cure at EOT.

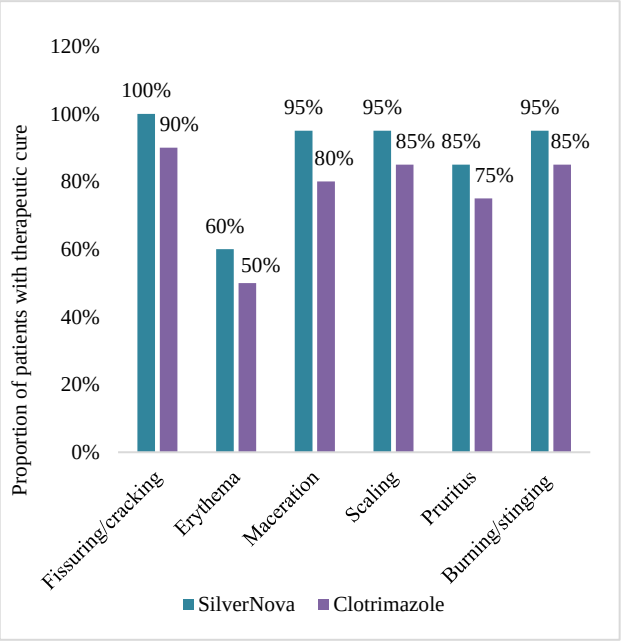

Figure 3: Proportion of intertrigo patients with therapeutic cure at EOT.

The proportion of patients with a therapeutic cure

At the end of the trial, a higher proportion of the patients with tinea infections reported a therapeutic cure in the SilverNova™ skin cream as compared to clotrimazole cream group. Figure 2 shows the proportion of tinea patients with therapeutic cures at EOT.

Similar outcomes were reported in the subgroup of patients with intertrigo. A higher proportion of the intertrigo patients treated with SilverNova™ skin cream reported a therapeutic cure at EOT as compared to clotrimazole group. Figure 3 shows the proportion of intertrigo patients with therapeutic cures at the end of the study.

Secondary endpoints

Self-assessed general health scoring

There was an improvement in general health scoring from baseline to EOT in both the treatment groups in patients with tinea infections (Table 4).

Initially, 60% of tinea patients in the treatment group rated their general health as unsatisfactory. By EOT, all tinea patients, whether using SilverNova™ / clotrimazole cream, reported their general health as very good, good/satisfactory. Larger proportion in SilverNova™ group scored their general health as "very good".

Table 1: Demographic data of the study participants.

Characteristics	Silvernova™ cream+clotrimazole cream (Test group)	Clotrimazole cream (Reference group)
Total participants	40	40
Male	21	20
Female	19	20
Mean age (In years)	39.48 (20.00-69.00)	38.75 (19.00-69.00)
Mean weight (Kg)	67.33 (48.00-85.00)	64.23 (48.00-84.00)
Mean height (cm)	161.60 (150.00-174.00)	161.43 (148.00-170.00)
Mean BMI (kg/m^2)	25.75 (20.03-32.02)	24.73 (18.67-32.41)

Table 2: Reduction of clinical signs and symptoms in patients with tinea.

Clinical signs and symptoms	Scoring	Silvernova™ cream + clotrimazole cream (Test Group) (%)		Clotrimazole cream (Reference group) (%)	
		Baseline	EOT	Baseline	EOT
Fissuring/cracking	0-None	10	95	0	85
	1-Mild	75	5	65	15
	2-Moderate	15	0	35	0
	3-Severe	0	0	0	0
Erythema	0-None	0	45	0	35
	1-Mild	0	55	0	55
	2-Moderate	80	0	85	10
	3-Severe	20	0	15	0
Maceration	0-None	30	95	15	80
	1-Mild	55	5	65	20
	2-Moderate	15	0	20	0
	3-Severe	0	0	0	0
Scaling	0-None	0	85	0	70
	1-Mild	20	15	50	30
	2-Moderate	80	0	50	0
	3-Severe	0	0	0	0
Pruritus	0-None	0	75	0	65
	1-Mild	0	20	0	35
	2-Moderate	55	5	70	0
	3-Severe	45	0	30	0
Burning/stinging	0-None	0	95	0	85
	1-Mild	15	5	15	15
	2-Moderate	75	0	80	0
	3-Severe	10	0	5	0

Table 3: Reduction of clinical signs and symptoms in patients with intertrigo.

Clinical signs and symptoms	Scoring	Silvernova™ cream + clotrimazole cream (Test group) (%)		Clotrimazole cream (Reference group) (%)	
		Baseline	EOT	Baseline	EOT
Fissuring/cracking	0-None	0	100	5	90
	1-Mild	70	0	60	10
	2-Moderate	30	0	35	0
	3-Severe	0	0	0	0
Erythema	0-None	0	60	0	50
	1-Mild	0	40	0	45
	2-Moderate	80	0	65	5
	3-Severe	20	0	35	0
Maceration	0-None	35	95	15	80
	1-Mild	55	5	80	20
	2-Moderate	10	0	5	0
	3-Severe	0	0	0	0
Scaling	0-None	0	95	0	85
	1-Mild	35	5	50	15
	2-Moderate	65	0	10	0
	3-Severe	0	0	0	0
Pruritus	0-None	0	85	0	75
	1-Mild	0	15	0	10
	2-Moderate	65	0	35	15
	3-Severe	35	0	65	0
Burning/stinging	0-None	0	95	0	85
	1-Mild	30	5	10	15
	2-Moderate	60	0	90	0
	3-Severe	10	0	0	0

Table 4: Self-assessed general health scoring in patients with tinea.

Score	Silvernova™ cream + clotrimazole cream (Test group) (%)		Clotrimazole cream (Reference Group) (%)	
	Baseline	EOT	Baseline	EOT
Very good	25	45	20	40
Good	15	50	20	50
Satisfactory	0	5	0	10
Unsatisfactory	60	0	60	0
Highly unsatisfactory	0	0	0	0

Table 5: Self-assessed general health scoring in patients with intertrigo.

Score	Silvernova™ cream + clotrimazole cream (Test group) (%)		Clotrimazole cream (Reference group) (%)	
	Baseline	EOT	Baseline	EOT
Very good	30	70	5	60
Good	25	20	55	35
Satisfactory	5	10	0	5
Unsatisfactory	35	0	40	0
Highly unsatisfactory	5	0	0	0

Improvement in general health scoring from baseline to EOT was also reported in the subgroup of patients with intertrigo (Table 5). All the patients scored the general health as very good, good, or satisfactory at EOT in both treatment groups. A higher proportion of patients in the SilverNova™ skin cream group scored general health as

very good.

On day 21 OF follow-up, more SilverNova™ cream-treated patients (85%) rated their general health as "very good" for tinea skin infection, surpassing clotrimazole-treated patients (70%). Both groups achieved favorable to very-good scores in Self-Assessment of General Health for intertrigo at the follow-up evaluation.

Safety outcomes

Both treatments demonstrated overall better safety and tolerability. All the reported adverse events were unlikely related to the study drug.

DISCUSSION

Despite therapeutic advances in the past years, the prevalence of fungal skin infections is still increasing.[22] Topical and systemic antifungal drugs, including azoles (itraconazole, fluconazole), terbinafine, and griseofulvin, are commonly used for the treatment of fungal skin infections.[13] However, these antifungal drugs have several limitations. These drugs need long-term adherence and have modest potency and efficacy due to the development of resistant strains and toxicity.[13,14] Fungal resistance to the different azoles appears very commonly.[23] The azole-containing oral antifungals have a wide range of side effects, including adverse hepatic effects, drug interactions, interference with the central nervous system, sex and thyroid hormones, and testosterone biosynthesis.[24] While, topical antifungals result in dryness of the skin and rashes.[25] A new topical treatment is needed to target fungi and bacteria causing secondary infections, minus harmful effects, improving current therapies.[24]

As mentioned earlier, resistance to antifungal treatment and skin barrier issues cause persistent Tinea infections. Antifungal resistance is a global concern, including in India.[26] In a study by Singh et al a dermatophytosis outbreak in India is linked to resistant trichophytons.[27] The study found high resistance rates in clinical Trichophyton isolates against commonly used oral antifungals including terbinafine, fluconazole, and griseofulvin. In another multicenter study, Tahiliani et al showed that the mean MIC of terbinafine is above the reference range in an Indian clinical setting.[12]

Skin barrier defects, like TEWL and reduced stratum corneum hydration, contribute to recalcitrant Tinea infections. In cases of tinea cruris, abnormal TEWL leads to lower cure rates and higher relapse rates after initial success.[15]

Treating tinea infections is complex due to different levels of host inflammatory response, causing erythema, swelling, pruritus, and burning. Scratching in response to itching damages skin, spreads infection, and slows healing, increasing the risk of bacterial superinfections.[16,17] Research indicates that both Gram-positive and Gram-negative bacteria contribute to superinfections in these cases, with *Staphylococcus aureus* being the most common culprit.[18] High susceptibility to bacterial superinfections can be addressed by choosing a topical therapy with proven efficacy as anti-inflammatory and broad spectrum anti-fungal and antibacterial activity, especially against *S. aureus*.

In recent years, nanotechnology has opened a new door for the development of nanosized inorganic and organic particles, which are finding several applications in medicine and therapeutics.[24] AgNPs have become one of the most interesting therapeutic choices for study because they have outstanding antimicrobial activity even at low concentrations.[26,28] Due to the strong inhibitory effect on a large spectrum of microbial species, AgNPs are widely studied for their clinical application.[29] AgNPs, either alone or in combination with other drugs, represent a promising therapeutic alternative against resistant microorganisms, as well as in complications associated with the use of antifungals.[20]

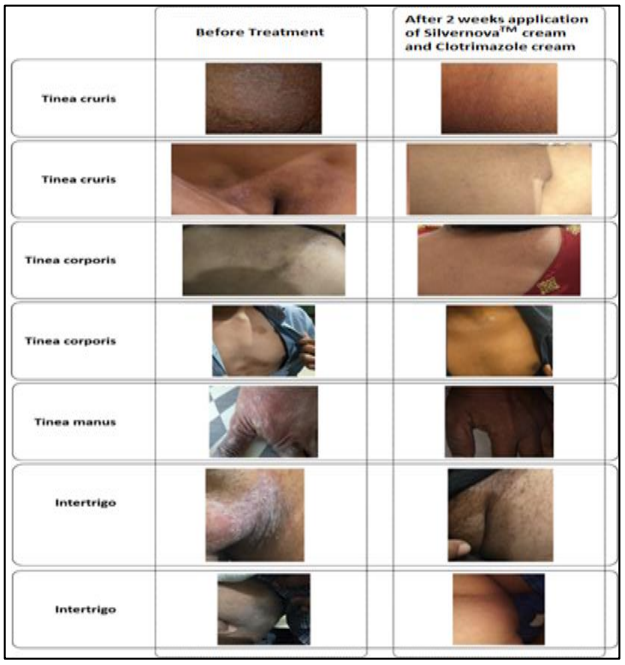

Figure 4: Representative images of patients treated with SilverNova™ skin cream.

Different mechanisms of AgNPs in retarding and inhibition of the dermatophytes are proposed, including the increase in cellular leakage, ergosterol reduction, and keratinase inhibition.[24] AgNPs are shown to reduce the ergosterol content in the fungal cell membrane in a way similar to azoles. AgNPs significantly decrease the activity of the CYP51 enzyme involved in ergosterol biosynthesis.[13] With the disruption of ergosterol biosynthesis, AgNPs alter cell membrane structure, thus

compromising membrane integrity and permeability and consequently interfering with fungal cellular growth and reproduction.[13,20] The reactive oxygen species (ROS) are produced at the surface of the silver nano-particles or by the released free silver ions. ROS disturbs several cellular processes and induces oxidative damage and hence is one of the proposed mechanisms for the antifungal activity of AgNPs.[24,30] AgNPs cause thinning of the fungal cell wall, agglutination of cellular proteins, rupture of the cell membrane, and leakage of intracellular components.[31,32] Keratinase enzymes play a key role in the pathogenesis of most dermatophyte fungi. Different species of dermatophytes produce different keratinolytic activities. It has been shown that the reduction in keratinase activities with the application of AgNPs is superior to that induced by standard antifungal agent.[24]

Antifungal studies have demonstrated that the AgNPs can inhibit the growth of several Candida species and are highly potent against Microsporum and Trichophyton dermatophytes, including *T. rubrum* and *T. mentagrophytes*. [3,32–35] Several studies have also elucidated the inhibitory effect of AgNPS against dermatophytes compared with the standard antifungal treatments. In these studies, dermatophytes were more sensitive to AgNPs than standard antifungals.[24,35,36]

Noorbakhsh et al investigated the effect of AgNPs alone and with fluconazole and griseofulvin on *T. rubrum*. They discovered that AgNPs enhanced antifungal effects when combined with fluconazole and griseofulvin.[37]

Mussin et al found that AgNPs, combined with ketoconazole, is effective against *M. furfur*. AgNPs enhance ketoconazole's antifungal action against *Malassezia* infections and superficial mycoses. The study suggests that AgNPs, when combined with other topical antifungals, can enhance treatment, decrease applications, and prevent recurrence.[20] There are also many reports on using silver nano-particles in antidandruff shampoos with effective antifungal activity. Ketoconazole complexed with silver nano-particles has a higher antidandruff activity against *M. furfur*.[9]

In addition to their antifungal properties, AgNPs possess anti-inflammatory effects, valuable for treating fungal skin infections with common skin inflammation. Research indicates that AgNPs modify the inflammatory response through various mechanisms. Recent studies highlight SilverSol®'s potent impact on various parasitic helminths.[38] The AgNP gel was effective in preventing biofilm formation by *S. mutans*, *S. sanguis*, and *S. salivarius*.[39] In another *in vitro* study, the AgNP gel in combination with betadine antiseptic solution was proven to be effective in inhibiting the growth of bacterial biofilms.[40] In the clinical study[41], the AgNP gel is shown to be effective in several oro-dental conditions including periodontitis and gingivitis. AgNPs disrupt the vascular endothelial growth factor (VEGF) pathway responsible for the T-helper type-2 (TH2) cell-mediated inflammation mediated by secretion of pro-inflammatory cytokines like IL-4, IL-5, IL-9, and IL-13.[21] It has been observed in animal models that AgNPs decrease inflammation markers such as tumor necrosis factor-alpha (TNF-a) and interleukin (IL)-6.[42]

In a pilot study, Kuruwa et al examined a colloidal nanosilver skin cream containing SilverSol®, coconut oil, vitamin E, and hyaluronic acid in tinea infection and intertrigo patients. The study found that when used alongside topical antifungals, the colloidal nanosilver skin cream notably decreased itching, burning, and bacterial infection associated with tinea infections within two weeks. Additionally, when applied with topical antifungal cream, the colloidal nanosilver skin cream expedited intertrigo healing within a two-week period.[43]

Taking into account these properties of AgNPs, SilverNova™ skin cream was investigated in individuals with tinea infections, seborrheic dermatitis, and intertrigo. Tinea corporis and tinea cruris usually appear as annular plaques resembling circular rashes with raised edges. Meanwhile, tinea pedis typically exhibits maceration or scaling between toes, evolving into chronic erythema with scaling.[4] Intertrigo has an insidious onset with symptoms such as itching, pain, burning, or prickling sensations in skin fold areas.[6] It is initially presented as mild, mildly erythematous papillae or plaques that may quickly progress to a more intense inflammation with erosions, oozing, exudation, maceration, and crusting.[44] Patients with seborrheic dermatitis have pink to red greasy-looking skin with yellowish flaky scales, accompanied by itching.[9] Our study demonstrated that SilverNova™ skin cream effectively reduces clinical manifestations such as fissuring/cracking, erythema, maceration, scaling, pruritus, and burning/stinging in individuals with tinea skin infections and intertrigo. Furthermore, a greater number of patients in the SilverNova™ skin cream group achieved therapeutic cure at EOT compared to the clotrimazole group.

Fungal skin diseases also affect the general health and quality of life of the patients.[45] In this study, participants self-assessed general health using a five-point scale of very good, good, satisfactory, unsatisfactory, and highly unsatisfactory at baseline and EOT. A clinically meaningful improvement was observed in SilverNovaTM skin cream-treated patients with tinea infections as well as intertrigo.

Earlier animal studies and clinical studies have demonstrated the safety of topical[46] as well as for human consumption of AgNPs at the therapeutic concentration and depending upon the particle size.[47,48] Increased surface-to-volume ratio in AgNPs also increases the potency of silver at reduced concentrations, further reducing the toxicity of silver particles depending on the size and shape of the nano-particles.[49] AgNPs are biocompatible with skin cells and do not exert toxicity

on human keratinocytes.[3] Studies have shown that AgNPs penetrate intact human skin *in-vivo* beyond the stratum corneum as deep as the reticular dermis; however, these nano-particles do not reach systemic circulation making AgNPs safe for topical application.[50] In the current study, no significant adverse effects were reported associated with SilverNova™ skin cream application.

In addition to colloidal nanosilver, SilverNova™ skin cream contains skin rejuvenating ingredients including coconut oil, vitamin E, and hyaluronic acid. Coconut oil offers anti-inflammatory effects by modulating cytokine levels and supporting skin healing. Moreover, its topical use enhances the stratum corneum's protective barrier functions and reduces TEWL, thus improving overall skin barrier function.[51] Vitamin E, an essential micronutrient, plays a crucial role in maintaining skin health due to its antioxidant properties. Research indicates that applying vitamin E enhances skin barrier elements, particularly ceramides in keratinocytes, thereby bolstering the skin's protective function. Additionally, its anti-inflammatory and photoprotective effects further supports overall skin well-being.[52] Conversely, hyaluronic acid plays a key role in maintaining skin's physiological function. As a natural moisturizing factor, it reduces TEWL and strengthens the skin barrier. Furthermore, it regulates tissue regeneration essential for wound healing. Topical application of hyaluronic acid yields anti-inflammatory benefits, mitigating excessive inflammation. Sustaining skin's structural integrity, bolstering its barrier function, and mitigating environmental damage are additional contributions of hyaluronic acid.[53]

Considering the overall outcomes of this study, it can be proposed that SilverNova™ skin cream has clinical application in the treatment of fungal skin infections, including tinea corporis, tinea cruris, tinea manus, tinea pedis infections, seborrheic dermatitis infection and Candida intertrigo as an adjuvant to topical and oral antifungals therapy. SilverNova™ skin cream not only has a broad antimicrobial action but also addresses the issue of epidermal barrier impairment and its protection leading to better management of recalcitrant infections. SilverNova™ skin cream has a broad-spectrum antimicrobial activity covering various fungi and bacteria in mixed infections in recalcitrant or chronic cases. It may also decrease the risk of bacterial superinfections by reducing pruritus and scratching due to its anti-inflammatory activity.

CONCLUSION

This study showed that SilverNova™ skin cream is effective and well-tolerated for the treatment of fungal skin infections. The topical application of SilverNova™ skin cream as an adjuvant has been shown to increase the efficiency of both topical and oral antifungals in the treatment of fungal skin infections yielding excellent results. It can be concluded that SilverNova™ is an innovative skin barrier repair cream with added properties of antibacterial, antifungal, anti-inflammatory, and optimum moisturizing effect and can be used as an adjuvant to oral and topical antifungals in the treatment of fungal skin infections.

Funding: Funding sources by Viridis BioPharma Pvt Ltd, Mumbai, India.
Conflict of interest: One of the authors, Anirudh Mehta is from Viridis BioPharma Pvt. Ltd., who manufacture and market SilverSol®. However, this has not affected the design of the study or interpretation of data anyway. The rest of the authors have no competing interests to declare.
Ethical approval: The study was approved by the Royal Pune Independent Ethics Committee for Jyoti Multispecialty Clinic and Mavens Institutional Ethics Committee for Maven's Hospital. This study was registered in Clinical Trials Registry- India (CTRI/2022/06/043512 Dated: 27/06/2022).

REFERENCES

1. Gunaydin SD, Arikan-Akdagli S, Akova M. Fungal infections of the skin and soft tissue. Curr Opin Infect Dis. 2020;33(2):130-6.
2. Kaushik N, Pujalte GGA, Reese ST. Superficial Fungal Infections. Prim Care. 2015;42(4):501-16.
3. Rónavári A, Igaz N, Gopisetty MK, Szerencsés B, Kovács D, Papp C, et al. Biosynthesized silver and gold nanoparticles are potent antimycotics against opportunistic pathogenic yeasts and dermatophytes. Int J Nanomed. 2018;13:695-703.
4. Kovitwanichkanont T, Chong AH. Superficial fungal infections. Aust J Gen Pract. 2019;48(10):706-11.
5. Taudorf EH, Jemec GBE, Hay RJ, Saunte DML. Cutaneous candidiasis - an evidence-based review of topical and systemic treatments to inform clinical practice. J Eur Acad Dermatol Venereol. 2019;33(10):1863-73.
6. Metin A, Dilek N, Bilgili SG. Recurrent candidal intertrigo: challenges and solutions. Clin Cosmet Investig Dermatol. 2018;11:175-85.
7. Kalra MG, Higgins KE, Kinney BS. Intertrigo and secondary skin infections. Am Fam Physician. 2014;89(7):569-73.
8. Janniger CK, Schwartz RA, Szepietowski JC, Reich A. Intertrigo and common secondary skin infections. Am Fam Physician. 2005;72(5):833-8.
9. Thomas LM, Khasraghi AH. Nanotechnology-Based Topical Drug Delivery Systems for Management of Dandruff and Seborrheic Dermatitis: An overview. Iraqi J Pharm Sci. 2020;29(1):12-32.
10. Lakshmanan A, Ganeshkumar P, Mohan SR, Hemamalini M, Madhavan R. Epidemiological and clinical pattern of dermatomycoses in rural India. Indian J Med Microbiol. 2015;33 Suppl:134-6.
11. Verma S, Madhu R. The Great Indian Epidemic of

Superficial Dermatophytosis: An Appraisal. Indian J Dermatol. 2017;62(3):227-36.
12. Tahiliani S, Saraswat A, Lahiri AK, Shah A, Hawelia D, Shah GK, et al. Etiological prevalence and antifungal sensitivity patterns of dermatophytosis in India – A multicentric study. Indian J Dermatol Venereol Leprol. 2021;87:800-6.
13. Abdallah BM, Rajendran P, Ali EM. Potential Treatment of Dermatophyte Trichophyton rubrum in Rat Model Using Topical Green Biosynthesized Silver Nanoparticles with Achillea santolina Extract. Molecules. 2023;28(4):1536.
14. Singh SB, Young K, Silver LL. What is an "ideal" antibiotic? Discovery challenges and path forward. Biochem Pharmacol. 2017;133:63-73.
15. Bhargava P, Nijhawan S, Singdia H, Mehta T. Skin Barrier Function Defect - A Marker of Recalcitrant Tinea Infections. Indian Dermatol Online J. 2020;11(4):566-9.
16. Hube B, Hay R, Brasch J, Veraldi S, Schaller M. Dermatomycoses and inflammation: The adaptive balance between growth, damage, and survival. J de Mycologie Médicale. 2015;25(1):e44- 58.
17. Gupta AK, Foley KA, Versteeg SG. New antifungal agents and new formulations against dermatophytes. Mycopathologia. 2017;182(1-2):127-41.
18. Sitepu EH, Muis K, Putra IB. Dermatophytes and bacterial superinfections in tinea pedis patients at Haji Adam Malik Central Hospital, Medan-Indonesia. Bali Med J. 2018;7(2):452-6.
19. Rengasamy M, Shenoy MM, Dogra S, Asokan N, Khurana A, Poojary S, et al. Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) Task Force against Recalcitrant Tinea (ITART) Consensus on the Management of Glabrous Tinea (INTACT). Indian Dermatol Online J. 2020;11(4):502-19.
20. Mussin JE, Roldán MV, Rojas F, de Los Ángeles Sosa M, Pellegri N, Giusiano G. Antifungal activity of silver nanoparticles in combination with ketoconazole against Malassezia furfur. AMB Express. 2019;9(1):131.
21. Agarwal H, Nakara A, Shanmugam VK. Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: A review. Biomed Pharmacother. 2019;109:2561-72.
22. Tripathy S. Rising prevalence of dermatophytosis in India: A matter of concern. Int J Infect Dis. 2016;45:318.
23. Howard SJ, Cerar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, et al. Frequency and evolution of Azole resistance in Aspergillus fumigatus associated with treatment failure. Emerg Infect Dis. 2009;15(7):1068-76.
24. Ouf SA, Mohamed AAH, El-Adly AA. Enhancement of the antidermatophytic activity of silver nanoparticles by Q-switched Nd:YAG laser and monoclonal antibody conjugation. Med Mycol. 2017;55(5):495-506.
25. Brewer AC, Huber JT, Girardo ME, Kosiorek HE, Burns MW, Stewart TD, et al. Cutaneous effects associated with fluconazole in patients treated for coccidioidomycosis. Int J Dermatol. 2019;58(2):250-3.
26. Talapko J, Matijević T, Juzbašić M, Antolović-Požgain A, Škrlec I. Antibacterial Activity of Silver and Its Application in Dentistry, Cardiology and Dermatology. Microorganisms. 2020;8(9):1400.
27. Singh A, Masih A, Monroy-Nieto J, Singh PK, Bowers J, Travis J, et al. A unique multidrug-resistant clonal Trichophyton population distinct from Trichophyton mentagrophytes/ Trichophyton interdigitale complex causing an ongoing alarming dermatophytosis outbreak in India: Genomic insights and resistance profile. Fungal Genet Biol. 2019;133:103266.
28. De Souza A, Mehta D, Leavitt RW. Bactericidal activity of combinations of silver–water dispersion with 19 antibiotics against seven microbial strains. Curr. Sci. 2006;91:926-9.
29. Pirtarighat S, Ghannadnia M, Baghshahi S. Green synthesis of silver nanoparticles using the plant extract of Salvia spinosa grown in vitro and their antibacterial activity assessment. J Nanostructure Chem. 2019;9(1):1-9.
30. Soni A, Kumar A, Kumar A, Choudhary A, Happy. New Era of Formulation as Silver Nanoparticles in Pharma. J Drug Deliv Ther. 2021;11(2-S):126-31.
31. El-Badry A, Assawah S, El-Kassas H, Hegab D, Amer D. New Remedy to Control Human Skin Fungal Infections by Silver Nanoparticles Biosynthesized by Two Marine Macro Algae. Egypt J Bot. 2019;49(2):493-511.
32. Kim KJ, Sung WS, Suh BK, Moon SK, Choi JS, Kim JG, et al. Antifungal activity and mode of action of silver nano- particles on Candida albicans. Biometals Int J Role Met Ions Biol Biochem Med. 2009;22(2):235-42.
33. Ayatollahi Mousavi SA, Salari S, Hadizadeh S. Evaluation of Antifungal Effect of Silver Nanoparticles Against Microsporum canis, Trichophyton mentagrophytes and Microsporum gypseum. Iran J Biotechnol. 2016;13(4):38-42.
34. Panja A, Mishra AK, Dash M, Pandey NK, Singh SK, Kumar B. Silver Nanoparticles – A Review. Eurasian J Med Oncol. 2021;5(2):95-102
35. Kim KJ, Sung WS, Moon SK, Choi JS, Kim JG, Lee DG. Antifungal effect of silver nanoparticles on dermatophytes. J Microbiol Biotechnol. 2008;18(8):1482-4.
36. Xia ZK, Ma QH, Li SY, Zhang DQ, Cong L, Tian YL, et al. The antifungal effect of silver nanoparticles on Trichosporon asahii. J Microbiol Immunol Infect. 2016;49(2):182-8.
37. Noorbakhsh F, Rezaie S, Shahverdi A. Antifungal Effects of Silver Nanoparticle alone and with Combination of Antifungal Drug on Dermatophyte Pathogen Trichophyton Rubrum. 2011;5:364-7.
38. Gajera G, Godse C, DeSouza A, Mehta D, Kothari

V. Potent anthelmintic activity of a colloidal nano-silver formulation (SilverSol®) against the model worm Caenorhabditis elegans. BMC Res Notes. 2023;16(1):130.
39. Tran PL, Luth K, Wang J, Ray C, de Souza A, Mehta D, et al. Efficacy of a silver colloidal gel against selected oral bacteria in vitro. F1000Res. 2019 Mar 7;8:267.
40. Tran P, Kopel J, Luth K, Dong H, Dev A, Mehta D, et al. The in vitro efficacy of betadine antiseptic solution and colloidal silver gel combination in inhibiting the growth of bacterial biofilms. Am J Infect Control. 2023;51(1):23-28.
41. Mahale S, Walvekar A, Tiwari S, et al. Efficacy of Colloidal Nano Silver Tooth Gel in the Management of Oro-Dental Conditions: A Prospective, Randomized, Triple Arm, Parallel, Double Blind Controlled Interventional Clinical Study. J Oral Health Comm Dent. 2023. (Accepted for publication).
42. Ong WTJ, Nyam KL. Evaluation of silver nanoparticles in cosmeceutical and potential biosafety complications. Saudi J Biol Sci. 2022;29(4):2085-94.
43. Kuruwa M, Pathak H, Mehta A, Jadhav SS. An open labeled multicentric pilot trial to study the safety and efficacy of colloidal nano silver skin cream in patients with various skin diseases. Biomed J Sci Tech Res. 2022;46(1):37040-48.
44. Mistiaen P, Poot E, Hickox S, Wagner C. Preventing and treating intertrigo in the large skin folds of adults: a literature overview. Dermatol Nurs. 2004;16(1):43-6,49-57.
45. Urban K, Chu S, Scheufele C, Giesey RL, Mehrmal S, Uppal P, et al. The global, regional, and national burden of fungal skin diseases in 195 countries and territories: A cross-sectional analysis from the Global Burden of Disease Study 2017. JAAD Int. 2020;2:22-7.
46. Gajbhiye S, Sakharwade S. Silver Nanoparticles in Cosmetics. J Cosmet Dermatol Sci Appl. 2016;06(01):48-53.
47. Pedersen G and Hegde BM. Silver Sol Completely Removes Malaria Parasites from the Blood of Human Subjects Infected with Malaria in an Average of Five Days: A Review of Four Randomized, Multi-Centered, Clinical Studies Performed in Africa. The Indian Practitioner. 2010;63(9):567-74.
48. De Souza A, Vora AH, Mehta AD, Moeller K. SilverSol® a Nano-Silver Preparation: A Multidimensional Approach to Advanced Wound Healing. In: (Eds.: Kumar P, Kothari V), Wound Healing Research, Springer. 2021:355-96.
49. Mihai MM, Dima MB, Dima B, Holban AM. Nanomaterials for Wound Healing and Infection Control. Materials. 2019;12(13):2176.
50. George R, Merten S, Wang TT, Kennedy P, Maitz P. In vivo analysis of dermal and systemic absorption of silver nanoparticles through healthy human skin. Australas J Dermatol. 2014;55(3):185-90.
51. Varma SR, Sivaprakasam TO, Arumugam I, Dilip N, Raghuraman M, Pavan KB, et al. In vitro anti-inflammatory and skin protective properties of Virgin coconut oil. J Tradit Complement Med. 2019;9(1):5-14.
52. Keen MA, Hassan I. Vitamin E in dermatology. Indian Dermatol Online J. 2016;7(4):311-5.
53. Dovedytis M, Liu ZJ, Bartlett S. Hyaluronic acid and its biomedical applications: A review. Eng Regen. 2020;1:102-13.

Cite this article as: Talathi A, Jadhav A, Purohit S, Mehta A. Efficacy and safety of SilverNova™ skin cream as adjuvant to oral and topical antifungals in treatment of fungal skin infections. Int J Res Med Sci 2023;11:3376-86.