

The Anti-Psoriatic Efficacy and Safety Profile of Topical and Intralesional Methotrexate: A Literature Review

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Abstract: Methotrexate (MTX) has long been considered the first-line oral systemic pharmacotherapy for psoriasis. The drug has several well-known systemic side effects, such as bone marrow suppression and hepatotoxicity. To avoid them, the use of topical or intralesional administrations of MTX has become an interesting option. With the advent of novel drug delivery systems, especially nanocarriers, the usage of a high-efficacy and safe topical MTX for psoriasis has nearly been attained. This review examined the development, anti-psoriatic efficacy and adverse effects of topical forms of MTX (plain MTX; MTX with chemical enhancer; MTX using nanotechnology; MTX with protein transduction domains; MTX with liquid crystalline systems; and MTX with physical enhancer/laser) and intralesional MTX in psoriasis patients and psoriasis-induced animals. The efficacy of topical MTX varied with the drug delivery technology employed. Nevertheless, the overall safety profile of the topical forms was favourable. A 25 mg/mL MTX solution injected intralesionally at the nail matrix worked well for nail psoriasis recalcitrant to topical treatment. To improve the standard of care for patients with psoriasis, randomized controlled trials that establish the most effective MTX-delivery system are needed.

Keywords: drug delivery, intralesional, liposome, methotrexate, psoriasis, topical

Introduction

Although biological agents are being increasingly used, sometimes as the first-line treatment for moderate-to-severe psoriasis, methotrexate (MTX) is still the cornerstone conventional systemic treatment for psoriasis. This drug has been approved for psoriasis treatment by United States Food and Drug Administration since 1972 and currently situated in the latest guideline as the primary treatment for moderate to severe psoriasis.^{1,2} It acts primarily by inhibiting dihydrofolate reductase enzyme, resulting in decreased DNA synthesis and cell proliferation.^{3,4} MTX has immunosuppressive and anti-inflammatory properties as it promotes T cell apoptosis and reduces tumour necrosis factor-alpha production.⁵ There is also evidence that it inhibits Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway signalling.⁶ All mechanisms lead to a reduction in inflammation and a decrease in epidermal hyperplasia in psoriasis.

The most common side effects that curtail the utilisation of oral MTX are nausea and/or vomiting. Moreover, the systemic administration of MTX carries a high risk of systemic side effects, such as bone marrow suppression and hepatotoxicity. Thus, topical and intralesional administrations of MTX are preferred as they can substantially reduce oral-MTX side effects.⁷ The initial major obstacle in developing a topical MTX was its physicochemical properties. MTX has hydrophilic properties, whereas the lipid constituents of the stratum corneum are lipophilic, which limits the permeation of hydrophilic molecules such as MTX.⁸ Moreover, MTX has a high molecular weight and exists in a dissociated form at physiological pH: this leads to low passive-diffusion, or a low skin-penetration ability.^{3,4}

Several drug delivery techniques—such as chemical and/or physical penetration enhancers, intralesional injection and nanocarrier drug-delivery systems—have been investigated and used to overcome the problem of the low skin-penetration ability of MTX. The results of those studies have varied between no benefits to a marked clinical improvement. The objective of the current study was to systematically review the efficacy of topical MTX (focusing on new drug-delivery systems) and intralesional MTX for psoriasis.

Methods

The Embase and Medline databases were searched from inception to July 2022 for English-language articles related to the research topic. The keywords related to “topical MTX”, “intralesional MTX” and “psoriasis”. To be considered for inclusion, studies had to investigate the anti-psoriatic efficacy of topical and/or intralesional MTX in psoriasis patients or an animal induced-mouse model of psoriasis. In all, 46 articles were retrieved. Ten of those related to topical MTX in an aqueous gel or cream, or with chemical enhancers (Table 1).^{9–18} Nineteen related to topical MTX with nanotechnology, supramolecular hydrogels, protein transduction domains and liquid crystalline systems (Table 2).^{8,19–36} Seven related to topical MTX with physical enhancers/laser/photodynamic therapy (Table 3).^{37–43} Eleven related to intralesional MTX injections (Table 4).^{15,44–53} Notably, 1 study conducted 2 experiments on the topical and intralesional treatment of psoriasis.¹⁵ Of the 46 articles, 27 were conducted on patients with psoriasis, whereas 19 used animal models of psoriasis.

Results and Discussion

Topical Plain MTX in Aqueous Cream or Gel

This platform was investigated in the early stages of topical MTX development. Topical plain MTX was produced by dissolving MTX in an aqueous cream or gel without using any enhancers or drug-assisted technology. Table 1 summarises 6 studies related to topical plain MTX in psoriasis.^{10–13,15,17} Three of those showed promising results: 1 case series; 1 randomized controlled trial (RCT); and 1 single-blind, placebo-controlled study.^{10,12,17} The remaining three showed ineffective results (1 intra-individual comparison, 1 RCT and 1 case series).^{11,13,15}

Fry et al and Stewart et al reported a small case series of topical plain MTX in patients with plaque psoriasis in years 1967 (n = 9) and 1972 (n = 9), respectively. Both used 0.2% MTX in aqueous cream with occlusion, but the duration of treatment was slightly shorter in the work by Stewart et al. Although Fry et al found that 90.4% of the patients demonstrated considerable improvements, Stewart et al demonstrated no clinical benefits. Skin irritation was found in 88.8% and 11.1% of the former and the latter studies, respectively.^{12,15}

Topical MTX gel formulations were developed later. Two of the four studies reported benefits from employing topical MTX gel to treat psoriasis.^{10,17} Syed et al (year 2001; n = 60) used 0.25% MTX in a hydrophilic gel twice daily for 4 weeks, and Eskicirak et al (year 2006; n = 40) used 1% MTX in hydroxymethylcellulose twice daily for 8 weeks in patients with chronic plaque-type psoriasis. Both studies compared the effects of MTX with placebos. Each investigation found a statistically significant higher number of patients achieved clinical improvements following MTX hydrogel therapy, compared with the placebo group (82.2% vs 4.3% in Syed et al's study, and 97.5% vs 60% in Eskicirak et al's study).^{10,17} In contrast, the results of topical plain MTX gel in other vehicle bases and for palmoplantar psoriasis were disappointing. Faghihi et al compared the efficacy of 1% MTX gel in a glycerine base with a placebo.¹¹ Glycerine is an inert substance and humectant, and it is commonly used as a vehicle in topical medications. Nevertheless, Faghihi et al's study did not find any significant differences in the clinical improvements shown by the treatment and placebo groups. Kumar et al studied the use of 0.25% MTX in a hydroxygel base twice daily for 12 weeks in 14 patients with palmoplantar psoriasis. The author concluded that, while the formulation was well tolerated, it was not very effective.¹³ The MTX gel did not induce any systemic or local adverse effects.

Topical MTX with Chemical Enhancer

The use of a chemical enhancer is one of the most convenient ways to facilitate the penetration of drugs into the stratum corneum. It disrupts the stratum corneum and then decreases the skin barrier resistance.^{54,55} Several chemical enhancers have been incorporated into topical MTX, such as carbamide (also known as urea), azone (also termed laurocapram) and

Table 1 Previous Studies Related to Topical Methotrexate (MTX) in Aqueous Cream or Gel, and to Topical MTX with Chemical Enhancers

Authors (Year)	Type of Study	Patient Number	MTX Formulation	Frequency of MTX Application	Duration of Treatment	Comparators	Results	Adverse Events (AE)
Topical plain MTX in aqueous cream or gel in human								
Fry et al (1967) ¹²	Case series	9	0.2% MTX in aqueous cream	Once daily with a polythene occlusive dressing for the 24 hours.	4–14 days (until clear, discomfort to continue, no continuing improvement)	-	Majority of patients (90.4%) had considerable improvement.	- Local AE: erythema, purpura (88.8%), ulceration (33.3%) - Systemic AE: No
Stewart et al (1972) ¹⁵	Intraindividual comparison	9	0.2% MTX cream under occlusion	N/A	5–7 days	Vanishing cream base	No improvement	- Local AE: erythema, superficial erosions, and burning sensation (11.1%) - Systemic AE: No
Syed et al (2001) ¹⁷	RCT	60	0.25% MTX in hydrophilic gel	Twice daily for 5 consecutive days/week	4 weeks (maximum of 40 topical applications in 4 weeks)	Placebo	Numbers of healed chronic plaques were higher in MTX group (82.2%) than in placebo group (4.3%), $P < 0.001$	- Local AE: No - Systemic AE: No
Eskicirak et al (2006) ¹⁰	SBPLC	40	1% MTX gel in hydroxymethylcellulose	Twice daily	8 weeks	Vaseline ointment	MTX gel was significantly more effective than placebo ($P < 0.01$).	- Local AE: No - Systemic AE: No
Faghihi et al (2012) ¹¹	RCT	65	1% MTX gel on glycerin base	Once daily	8 weeks	Placebo	No improvement	- Local AE: N/A - Systemic AE: N/A
Kumar et al (2004) ¹³	Case series	14 PPP*	0.25% MTX in a hydroxygel base	Twice daily	12 weeks	-	Not very effective (42% of patients had at least 50% improvement)	- Local AE: No - Systemic AE: No
Topical MTX with chemical enhancer in human								
Bjerring et al (1986) ⁹	DBPLC	5	0.25% MTX cream in carbamide base	Twice daily	3 weeks	Placebo	No clinical and histological effects	- Local AE: N/A - Systemic AE: No

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Table 1 (Continued).

Authors (Year)	Type of Study	Patient Number	MTX Formulation	Frequency of MTX Application	Duration of Treatment	Comparators	Results	Adverse Events (AE)
Weinstein et al (1989) ¹⁸	DBPLC	42	0.1%, 0.5%, and 1% of MTX in a laurocapram-containing gel	Twice daily	6 weeks	Vehicle	At least 50% improvement was found in 60%, 59%, 50%, and 25% of patients with 0.1% MTX, 0.5% MTX, 1% MTX, and vehicle, respectively.	- Local AE: Some patients had mild irritation and temporary burning sensation. - Systemic AE: No
Sutton et al (2001) ¹⁶	DBPLC	53	1% MTX in laurocapram (azone) gel formulation	Once daily	8 weeks	Placebo	Marked, moderate, and slight improvements were found in 27%, 7%, and 44% of MTX in azone, respectively. The majority (59%) of patients with placebo were only slight improved.	- Local AE: mild to moderate degree of pruritus, burning, irritation, and eruption (69.8%). - Systemic AE: headache (unlikely to related to treatment)
Ravi Kumar et al (1999) ¹⁴	Case series	16 PPP*	1% MTX gel in propylene glycol	Twice daily	8 weeks	-	At least 50% improvement was obtained in 80% and 64% of patients with palmar and plantar psoriasis patients, respectively.	- Local AE: No - Systemic AE: No

Abbreviations: DBPLC, double-blind, placebo-controlled study; N/A, not available; PPP*, palmoplantar psoriasis; RCT, randomized, controlled study; SBPLC; single-blind, placebo-controlled study.

Table 2 Topical Methotrexate (MTX) Using Nanotechnology and Protein Transduction Domain

Authors (Year)	Type of Study	Patient Number	MTX Formulation	Frequency of MTX Application	Duration of Treatment	Comparators	Results	Adverse Events (AE)
Topical MTX using nanotechnology in human								
Lakshmi et al (2007) ²⁵	RCT	30	0.25% niosomal MTX incorporated chitosan gel	Once daily	12 weeks	a. Marketed 0.25% MTX gel b. Placebo	- Niosomal MTX gel and marketed MTX gel were superior to placebo (<i>P</i> < 0.05). - Niosomal MTX gel was more efficacious than marketed MTX gel.	- Local AE: No - Systemic AE: No
Vanaja et al (2008) ³⁰	Open-label randomized parallel study	25	Ultra-deformable 0.25% liposomal MTX gel	N/A	10 weeks	1% plain MTX gel	- Liposomal MTX gel had comparable reduction in disease severity (45.3%), comparing to plain MTX gel (46.6%).	- Local AE: No - Systemic AE: No
Topical MTX using nanotechnology in animal mouse-model of psoriasis								
Authors (Year)	N	MTX Formulation and Frequency of Application	Comparators	Duration of Treatment	Results	Adverse Events (AE)		
Bahramizadeh et al (2019) ²¹	72	MTX-entrapped deformable liposomes containing oleic acid in 3 concentrations a) 0.05% MTX daily b) 0.1% MTX daily c) 0.1% MTX every other day	d) Empty liposomes daily e) MTX subcutaneous injection single dose f) Betamethasone lotion daily g) MTX containing 0.1% carbomer gel daily h) Disease group with no treatment	7 days	Clinical: Among 3 concentrations of liposomal MTX, PASI score was decreased by 0.05% MTX liposome while it was increased by 0.1% MTX liposome. Histology: The reduction of epidermal thickness was only significantly in groups a, b (0.05% and 0.1% MTX-liposome daily) and f (betamethasone lotion daily). However, the inflammation index was significantly reduced in groups a-f. Cytokines: -	- Local AE: N/A - Systemic AE: No		
Chandra et al (2019) ²³	12	a) 0.25% MTX-incorporated with ethosomal gel and 2% salicylic acid daily	b) Blank gel (Vaseline) c) Disease group with no treatment	7 days	Clinical: PASI scores decreased from 4 to 1, and from 4 to 3, in MTX ethosomal group and blank gel group, respectively. PASI score was not changed in the disease group with no treatment. Histology: MTX ethosomal gel treated group showed normal skin with very mild dyskeratosis. Blank gel treated group displayed moderate to high hyperkeratosis and orthokeratosis. Cytokines: -	- Local AE: N/A - Systemic AE: N/A		

Authors (Year)	N	MTX Formulation and Frequency of Application	Comparators	Duration of Treatment	Results	Adverse Events (AE)
Yang et al (2021) ³⁶	48	a) MTX/nicotinamide cerosomes (0.05% w/ v and 6% w/v) daily	b) MTX/nicotinamide (0.05% w/ v and 6% w/v) solution c) MTX suspension (0.05% w/v) d) Oral MTX dose equivalent to 7.5 mg/ week for human e) Nicotinamide solution (6% w/ v) f) Blank cerosomes g) Imiquimod cream h) Normal control	7 days	Clinical: PASI score in MTX/nicotinamide cerosomes group was significantly lower than other treatment group ($p < 0.01$). Histology: Epidermal thickness in MTX/nicotinamide cerosomes group was significantly lower than other treatment groups ($p < 0.001$) Cytokines: MTX/nicotinamide cerosomes group exhibited the best effects in downregulating the levels of several proinflammatory cytokines.	- Local AE: N/A - Systemic AE: N/A
Panonnummal et al (2018) ²⁸	N/A	a) 100 $\mu\text{g}/\text{cm}^2$ MTX loaded chitin nanogel (MCNG) b) 150 $\mu\text{g}/\text{cm}^2$ of MCNG	c) 150 $\mu\text{g}/\text{cm}^2$ of MTX in carbopol gel d) Carbopol gel e) Control chitin nanogel f) Disease induced group with no treatment	3 weeks	Clinical: There was a significant reduction in PASI score by MCNG at both 150 $\mu\text{g}/\text{cm}^2$ dose (89.2%) and 100 $\mu\text{g}/\text{cm}^2$ dose (73.1%), compared to 33.9% reduction in PASI score in 150 $\mu\text{g}/\text{cm}^2$ of MTX in carbopol gel. Histology: MCNG treated group displayed less inflammatory cell infiltration, intact of granular layer, absence of parakeratosis and no micro abscess. MTX in carbopol gel and carbopol gel treated groups exhibited features of psoriasis histology such as regular acanthosis, intraepidermal neutrophilic abscess. Cytokines: -	- Local AE: No - Systemic AE: No
Asad et al (2021) ³²	25	a) MTX nanoparticles embedded into chitosan hydrogel	b) Free MTX hydrogel c) Marketed cream d) Imiquimod cream e) Normal control	10 days	Clinical: PASI score was decreased in group a-c, but a mark decreased was observed in group a Histology: Group a-c displayed the improvement in psoriatic lesion. Group b showed decrease in the thickness of both the dermis and epidermis but leukocytic infiltrations were present. Group c displayed a noticeable reduction in psoriatic lesions with better hyperkeratosis and parakeratosis feature. Group a showed a healthy keratin layer with decreased parakeratosis and hyperkeratosis level Cytokines: Group a showed better result in the reduction of $\text{TNF-}\alpha$ and IL-6, compared to group b and c.	- Local AE: N/A - Systemic AE: N/A

Avasatthi et al (2016) ²⁰	30	a) MTX-loaded nanostructured lipid carrier (MTX-NLC) gel Frequency: not available	b) MTX gel formulation c) Blank gel d) Disease induced group with no treatment e) Disease free control group with no treatment	7 days	Clinical: MTX-NLC gel showed highest reduction in average PASI score, followed by MTX gel and blank gel. Histology: Normal skin structure with very mild keratosis was found in MTX-NLC gel treated group whereas few hyperkeratosis and parakeratosis was exhibited in MTX gel treated group. Cytokines: -	- Local AE: N/A - Systemic AE: N/A
Agrawal et al (2020) ¹⁹	24	a) MTX loaded nanostructured lipid carriers (MTXNLC) in carbopol gel daily	b) MTX in carbopol gel c) Disease group with soft paraffin d) No disease with soft paraffin	6 days	Clinical: The MTXNLC gel and MTX gel exhibited comparable efficacy of reduction in PASI score Histology: MTXNLC gel provided significant improvement in psoriatic histological alteration which was better than MTX gel Cytokines: MTXNLC showed significant decrease inflammatory cytokines including TNF- α , IL-1 β and IL-6 which was better than MTX gel.	- Local AE: N/A - Systemic AE: N/A
Amarji et al (2016) ⁸	24	a) 0.25% MTX loaded microemulsion in poloxamer gel daily	b) 0.1% topical dexamethasone c) Poloxamer gel with no active drug d) No treatment	5 days	Clinical: PASI score was significantly reduced in MTX loaded microemulsion in poloxamer gel ($P < 0.001$) from third day onwards whereas no cure was observed in groups c and d. Nevertheless, 0.1% dexamethasone showed the statistically most significant anti-psoriatic effect from second day onwards. Histology: - Cytokines: -	- Local AE: no irritation - Systemic AE: N/A
Rajitha et al (2019) ²⁹	36	a) MTX loaded nanoemulsion gel in Chaulmoogra oil (MTX-NE) daily	b) Bare nanoemulsion gel, daily for 1 month c) Chaulmoogra oil, daily for 1 month d) Oral MTX tablet, once weekly for 1 month e) Disease group with no treatment f) No disease with no treatment	1 month	Clinical: MTX-NE showed highest average reduction in PASI score (95%), which was higher and even better than oral MTX group (91%). On the other hand, bare nanoemulsion gel and Chaulmoogra oil provided 70% and 46% reductions in PASI score. Histology: MTX-NE and oral MTX normalized epidermal thickness to the same level of normal skin (group f), which was significantly different from the bare nanoemulsion gel, Chaulmoogra oil, and disease groups. Cytokines: -	- Local AE: N/A - Systemic AE: N/A (low level of drug accumulation in vital organs with MTX-NE in comparison with oral MTX).

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Table 2 (Continued).

Authors (Year)	N	MTX Formulation and Frequency of Application	Comparators	Duration of Treatment	Results	Adverse Events (AE)
Rashid et al (2021) ³⁴	36	a) Olive oil based MTX loaded nanoemulsion gel (MTX NEG) daily	b) MTX plain gel c) Oral MTX tablet, once weekly for 1 month d) Olive oil e) Imiquimod cream f) Normal control	28 days	Clinical: MTX NEG and oral MTX demonstrated the highest percentage of PASI score reduction after 28 days (94.9% and 91.7%, respectively) While MTX plain gel and olive oil reduced PASI score by 61.3%, and 45.9%, respectively. Histology: - Cytokines: -	- Local AE: N/A - Systemic AE: N/A
Fratoddi et al (2019) ²⁴	16	a) Gold nanoparticles functionalized with sodium 3-mercaptopropene sulphonate (AuNPs-3MPS) loaded with MTX daily b) AuNPs-3MPS loaded with MTX daily	c) AuNPs-3MPS without MTX once daily for 2 days d) AuNPs-3MPS without MTX once daily for 1 day	a) 2 days b) 1 day	Clinical: AuNPs-3MPS loaded with MTX showed significant reduction in scaling and erythema scores, compared with AuNPs-3MPS alone. Histology: AuNPs-3MPS loaded with MTX displayed a reduction of epidermal thickness, parakeratosis and hyperkeratosis, compared with AuNPs-3MPS without MTX. Cytokines: -	- Local AE: No skin irritation - Systemic AE: No
Özcan et al (2020) ²⁷	53	a) MTX coupled with gold nanoparticles (MTX-GNPs) gel daily (MTX 12.5 mg/week)	b) MTX gel (12.5 mg/week) c) Gold nanoparticles (GNPs) gel d) Carbopol 980 gel carrier e) Disease group with no treatment f) No disease with no treatment	7 days	Clinical: MTX-GNPs showed significant reduction of ear inflammation, which was higher than GNPs gel. MTX gel lacked efficacy, despite the high dose, in reducing ear inflammation. Histology: MTX-GNPs exhibited uninflamed histologic feature, which was similar to the no-disease group. MTX gel and GNPs gel displayed features of psoriatic phenotype. Cytokines:	- Local AE: N/A - Systemic AE: No
	14	a) MTX-GNPs gel daily	b) Topical calcipotriol-betamethasone c) Vaseline	2 weeks	Clinical: - Histology: MTX-GNPs inhibited skin hyperplasia (acanthosis and papillomatosis) significantly better than topical calcipotriol-betamethasone Cytokines:	- Local AE: N/A - Systemic AE: N/A
Limon et al (2019) ²⁶	6	MTX in nanostructured supramolecular hydrogel every other day	MTX sodium salt in water (at the same concentration)	10 days	Clinical: MTX supramolecular hydrogel showed a decreased in ear thickness (50% reduction) from Day 8, while MTX solution showed a similar decrease at Day 11. Histology: - Cytokines: -	- Local AE: No skin rigidity, no hair loss, no exudate - Systemic AE: N/A

Xu et al (2022) ³⁵	36	a) MTX-Zinc oxide/Ag (ZA) embellished with nanomicelles (NMs) and further embedded with carbopol(Car); (Car@NMs@MTX-ZA hydrogels), therapeutic dosage: 0.5 mL/daily	b) Car@NMs@MTX hydrogel c) Car@NMs@ZA hydrogel d) Car@MTX hydrogel e) Car@ZA hydrogel f) Car@MTX-ZA hydrogel g) Zinc oxide h) Blank carbopol hydrogel i) Negative control	6 days	Clinical: Car@NMs@MTX-ZA hydrogels showed the highest reduction in PASI score. Histology: Car@NMs@MTX-ZA hydrogels displayed the highest reduction in epidermal thickness and HE Baker grading. Cytokines: The mRNA and protein expressions of TNF- α , IL-23, IL-1 β and IL-6 was prominently suppressed by Car@NMs@MTX-ZA hydrogels compared with the other groups	- Local AE: N/A - Systemic AE: N/A
Topical MTX using protein transduction domains or cell-penetrating peptides						
Byamba et al (2014) ²²	30	a) 0.1% topical skin-permeable MTX (SP-MTX) daily b) 1% topical SP-MTX daily	c) Disease free control group and disease induced group d) Intraperitoneal MTX treatment (IP-MTX) e) No treatment	3 days	Clinical: The cumulative PASI score was lowest in the 1% SP- MTX treatment group, followed by IP-MTX and 0.1% SP- MTX Histology: The increase in epidermal thickness was improved (compared with baseline) by intraperitoneal MTX and both concentrations of skin-permeable MTX (dose dependent). Cytokines: 1% SP-MTX almost completely reduced IL-17A-producing $\gamma\delta$ T cell. IP-MTX partially reduced and 0.1% SP-MTX barely affected IL-17A-producing $\gamma\delta$ T cell.	- Local AE: N/A - Systemic AE: No
Topical MTX using liquid crystalline systems						
Bernandes et al (2021) ³³	42	a) MTX-loaded lamellar liquid crystal systems daily b) MTX-loaded hexagonal liquid crystal systems daily	c) MTX hydrogel daily d) 0.1% dexamethasone cream e) Negative control f) Imiquimod cream	5 days	Clinical: Erythema improved in the groups a, c, d. Peeling improved in the groups c, d. The lesion area improved in the groups a, c, d and f Histology: Group a, b, f showed the higher thickening of the epidermis compared to c, d, e groups (P <0.05). Cytokines: Group a, b, f showed higher cyclooxygenase-2 and myeloperoxidase activity and prostaglandin-2 production compared to the c, d, e groups (P <0.05) Group a, b showed higher level of IL-1 and IFN- γ in the skin of animals when compared with group d, e, f	- Local AE: N/A - Systemic AE: N/A
Alves et al (2022) ³¹	35	a) Cholesterol/ceramide-based MTX-loaded liquid crystals daily b) Cholesterol-based MTX-loaded liquid crystals daily	c) Dexamethasone acetate d) Negative control e) Imiquimod cream	3 weeks	Clinical: - Histology: Both MTX-loaded liquid crystals formulation exhibited an increase in keratinization score, epidermis thickness, and inflammatory infiltrate. Cytokines: Both MTX-loaded liquid crystals formulations upregulated several pro-inflammatory cytokines (IL-1, IFN- γ , TNF- α)	- Local AE: N/A - Systemic AE: N/A

Table 3 Previous Studies Related to Topical Methotrexate (MTX) with Physical Enhancers/Laser/Photodynamic Therapy

Authors (Year)	Type of Study	Patients	MTX Formulation and Application	Assisted MTX Penetration	Comparators	Frequency of MTX Application	Duration of Treatment	Results	Adverse Events (AE)
Topical MTX with laser assisted-drug delivery/photodynamic therapy									
Ali et al (2008) ³⁷	RCTs	30	0.25% liposomal MTX hydrogel with occlusive patch	650-nm diode laser (80 joules after MTX application and then 3 times/ week)	a. Plain MTX gel b. placebo	Once daily under occlusion for 30 minutes	12 weeks	- Complete clearance was found in 46.6% and 13.3% of patients with liposomal MTX and plain MTX gel, respectively. There was no improvement in placebo-treated lesions.	- Local AE: No - Systemic AE: No
Ramez et al (2018) ⁴¹	Intraindividual comparison	30	0.1% nanoparticulated MTX microemulsion based on jojoba oil	Fractional erbium:YAG laser	MTX microemulsion based on jojoba oil without laser assisted	3 times weekly	8 weeks	Macroemulsion/laser combination yielded a higher significant reduction in disease severity. ($P < .05$).	- Local AE: N/A - Systemic AE: No
Wang et al (2022) ⁴³	RCTs (mouse)	56	MTX and 5-aminolevulinic acid (MTX-ALA) nanogels daily	635 nm laser (photodynamic therapy; PDT)	a) Topical 0.05% MTX-10% 5-ALA suspension + PDT b) Topical 10% ALA solution + PDT c) Topical 10% 5-ALA solution and oral 0.2 mL of the MTX suspension + PDT d) Oral 0.2 mL of the MTX suspension e) Imiquimod cream f) Normal control	Daily	7 days	Clinical: MTX-ALA nanogels + PDT exerted the best effect in decreasing the PASI score, compared to other groups. Histology: MTX-ALA nanogels + PDT; oral MTX; and oral MTX plus topical ALA + PDT group displayed the decreased of the thickened epidermis and alleviated inflammatory cell infiltration Cytokines: Only MTX-ALA nanogels + PDT can normalize TNF- α and IL-17A levels to those of normal control group	- Local AE: No skin erythema and no change in transepidermal water loss in MTX-ALA nanogels mouse - Systemic AE: No histopathological changes in liver and kidney of mouse except in oral MTX group

Topical MTX with iontophoresis									
Tiwari et al (2003) ⁴²	Intraindividual comparison	1 PPP*	MTX disodium solution (10 mg/ml)	Cotton gauze soaked in MTX solution with iontophoresis (12-15 mA)	No treatment	Once a week	4 weeks	The treated side had > 75% improvement while there was no clinical change on the control site.	- Local AE: No - Systemic AE: No
Haseena, et al (2017) ⁴⁰	Intraindividual comparison	28 PPP*	MTX solution (50 mg/2 ml) dissolved in 50 ml of water: approximately a total of 1 mg/ml of MTX)	Gauze soaked in MTX solution (1mg/ml) on the palm/sole that covered with aluminum foil plus iontophoresis (5-10 mA). White soft paraffin was applied on the other days.	White soft paraffin and iontophoresis. Coal tar ointment was applied on the other days.	Once weekly (4 sessions) and every 2 weeks (2 sessions)	8 weeks	- MTX solution significantly reduced disease severity (63.94%), comparing to the control (47.66%).	- Local AE: No - Systemic AE: No
Andanooru Chandrappa et al (2020) ³⁸	Open label study	50 PPP*	3-4 ml of 15 mg/ml MTX solution	Gauze soaked in MTX solution with iontophoresis (4.5 mA)	0.05% clobetasol propionate ointment twice daily	Once weekly	6 weeks	- There was no statistically significant difference in improvement between MTX and clobetasol groups.	- Local AE: Trivial and self-limiting burn injury (48%) - Systemic AE: No
Topical MTX with microneedle patch made of hyaluronic acid in animal models of psoriasis									
Du et al (2019) ³⁹	30	3 doses of MTX sodium aqueous solutions a) low dose (6.5 µg of MTX), b) medium dose (13.8 µg of MTX) c) high dose (30.6 µg of MTX) with dissolving microneedle patch made of hyaluronic acid (HA) daily for 5 days		d) blank HA microneedle patch e) disease group with no treatment f) disease free control group with no treatment Daily for 5 days		Clinical: The medium and high doses MTX with microneedle patch caused improvement. No improvement with blank HA microneedle application. Histology: Epidermal thickness was improved in all doses of MTX microneedle patch, especially in the medium dose and high dose MTX microneedle patches. Cytokines: IL-23 and IL-17 were downregulated by the MTX microneedle patch in a dose dependent manner.			- Local AE: N/A - Systemic AE: No
	25	a) MTX sodium aqueous solutions at medium dose (13.8 µg of MTX) with dissolving microneedle patch made of HA daily for 5 days		b) oral MTX (13.8 µg of MTX) c) oral MTX (27.6 µg of MTX) d) disease group with no treatment e) disease free control group with no treatment with dissolving microneedle patch made of HA daily for 5 days		Clinical: At the same MTX dosage (13.8 µg), MTX microneedle patch was superior to oral MTX in reducing psoriasiform dermatitis. Histology: Medium dose MTX microneedle patch and double dose of oral MTX exhibited comparable efficacy in reduction of epidermal thickness. Comparing to oral MTX, the thickness was reduced more in MTX microneedle with the same MTX dose. Cytokines: -			- Local AE: N/A - Systemic AE: No

Abbreviations: mA, milliampere; N/A, not available; PDT, photodynamic therapy; PPP*, palmoplantar psoriasis.

Table 4 Previous Studies Related to Intralesional Methotrexate (MTX) Injections

Author (Year)	Type of Study	Patients (Lesions)	Injection Site	MTX Dosage	Comparators	Frequency	Treatment Duration	Efficacy of MTX Group	Adverse Events of MTX
Stewart et al (1972) ¹⁵	Intra-individual comparison	9 (45)	Plaque psoriasis	a) 0.1 ml of 0.5% MTX sodium solution (0.5 mg MTX)	b) 0.1 ml of 0.5% MTX sodium and 0.3% calcium leucovorin solution c) 0.1 ml sterile saline d) topical 5 mg of MTX sodium solution under occlusion e) occlusion of the skin without topical medication	- a, b and c. injected intralesionally every 12 hours for 36-hour period weekly - d. daily - e. continuous	3 weeks	No significant improvement in the areas treated by topical or intralesional methods	- Local AE: N/A - Systemic AE: Mild degree of transaminitis (11.1%)
Saricaoglu et al (2011) ⁵⁰	Case report	1 (1)	Nail matrix	2.5 mg MTX solution	-	Weekly	6 weeks	Improvement in subungual hyperkeratosis and pitting nails	- Local AE: No - Systemic AE: No
Grover et al (2017) ⁴⁶	Prospective study	4 (30)	Nail bed	0.1 mL of MTX 25 mg/mL	-	5 injections with an interval of 3 weeks.	15 weeks	There was a significant reduction in nail psoriasis severity index after MTX injections ($P < 0.001$).	-Local AE: pain, injection site pigmentation, nail bed hemorrhage - Systemic AE: No
Mittal et al (2018) ⁴⁸	Prospective, unblinded study	17 (90)	Nail matrix	a) 0.1 ml of MTX 25 mg/ml	b) 0.1 ml of 10 mg/ml triamcinolone acetoneide, c) 0.1 ml of 50 mg/ml cyclosporine	2 injections with an interval of 6 weeks.	6 weeks	The efficacy of MTX was superior to cyclosporine but it was comparable to triamcinolone acetoneide.	-Local AE: transient post-injection numbness (20%), pain (3.3%), Systemic AE: N/A
Mokni et al (2018) ⁴⁹	Case report	1 (6)	Nail matrix	0.1 ml of MTX 5 mg/2ml	-	Monthly	3 months	Nail dystrophy completely resolved except filiform hemorrhage.	- Local AE: N/A - Systemic AE: No

Duarte et al (2019) ⁴⁵	Case report	2 (2)	Nail matrix	0.1 ml of MTX 25 mg/ml	-	Every 30 days	3 months	Improvement	- Local AE: N/A - Systemic AE: N/A
Jindal et al (2020) ⁴⁷	Case report	1 (1) ACH	Nail matrix	0.2 ml of MTX 5 mg/ml	-	Monthly	4 months	Completely disappear of lesion	- Local AE: N/A - Systemic AE: N/A
Choudhary et al (2021) ⁴⁴	Prospective study	20 (89)	Nail matrix	2.5 mg	-	Weekly	6 weeks	NAPSI score decrease significantly from 3.70 (baseline) to 0.67 at 12 weeks.	- Local AE: Pain at injection site (10%), acute paronychia (5%) - Systemic AE: No
Starace et al (2022) ⁵³	Prospective study	12 (20)	Nail matrix	0.1 ml of MTX 25 mg/ml	0.1 ml of 10 mg/ml triamcinolone acetonide	4 injections with an interval of 6 weeks.	24 weeks	Nail psoriasis responded well to both treatment but more stability was noted at follow-up period in MTX group	- Local AE: Subungual hematoma - Systemic AE: N/A
Alakad et al (2022) ⁵²	RCT	28 (123)	Nail matrix and nail bed	0.02 ml of MTX 25 mg/ml	Fractional CO ₂ laser followed by topical application of 0.1 mL of MTX 25 mg/mL	Biweekly for 6 treatment sessions	3 weeks	Both treatments were associated with statistically significant improvement of nail psoriasis score. No statistically significant difference between both treatments was found.	- Local AE: Subungual hematoma and pain was less significantly found in Fractional CO ₂ group - Systemic AE: N/A
Abdelmeniem et al (2022) ⁵¹	RCT	60	Nail matrix and nail bed	a) 0.1 ml of MTX (50 mg/2 ml)	b) 0.1 ml of 5-FU (250 mg/5 ml) c) 0.1 ml of triamcinolone acetonide (10 mg/ml) d) topical 0.005% calcipotriol cream plus 20% urea under occlusion twice daily	Monthly	3 months	The mean percentage of NAPSI improvement was highest in topical calcipotriol plus urea group, followed by intralesional triamcinolone, MTX and 5-FU.	-Local AE: Subungual hematoma, tolerable pain - Systemic AE: N/A

Abbreviations: ACH, acrodermatitis continua of Hallopeau; FU, fluorouracil; NAPSI, Nail Psoriasis Severity Index; N/A, not available; RCT, randomized, controlled study.

propylene glycol. Carbamide increases the permeability of the stratum corneum by raising the amount of water absorbed by corneocytes and dissociating corneocyte adhesion (at high concentrations of carbamide).⁵⁶ Azone is a polymeric chemical enhancer which can cause fluidisation and disruption of the liposomal lipids of the skin. Integrating azone into topical MTX can enhance both lipophilic and hydrophilic drug delivery to the skin.⁵⁷ Propylene glycol is a hydrophilic molecule which increases drug permeation by improving the partition properties of active drugs in the skin.⁵⁴

Four studies explored the use of topical MTX with a chemical enhancer. Three were double-blind, placebo-controlled trials: one investigated topical MTX with carbamide, while two considered azone gel. The fourth work, a case series, examined propylene glycol (Table 1).^{9,14,16,18} In 1986, Bjerring et al showed that 0.25% MTX cream with a carbamide base failed to demonstrate either clinical or histological improvements in 5 patients with plaque-type psoriasis.⁹ Weinstein et al (0.1%, 0.5%, 1% MTX) and Sutton et al (1% MTX) investigated topical MTX in an azone gel vehicle at different concentrations, ranging from 0.1% to 1%, in patients with plaque-type psoriasis.^{16,18} Both studies showed a superior efficacy of MTX in the azone gel than a placebo. With the MTX-treatment groups, the efficacy was not related to the concentration of MTX. Skin irritation was the common side effect of the azone-containing formulation.^{16,18} In 1999, Ravi Kumar et al showed clinical improvement in 80% and 64% of patients with palmar and plantar psoriasis, respectively, by using 1% MTX in propylene glycol. No local or systemic side effects were reported.¹⁴

Although three of the four studies showed clinical benefits from the use of topical MTX with a chemical enhancer, there are some difficulties associated with its use in practice. As the macromolecular weight of MTX is quite high, a high concentration of chemical enhancer is needed to permeate the skin effectively, resulting in skin irritation.⁵⁸

Topical Methotrexate Using Nanotechnology

In recent years, nanoscale drug delivery systems, or drug nanocarriers, have developed rapidly. This technology greatly enhances the efficacy of transdermal drug delivery. It uses nanomaterial as a transporter to carry an active drug to a target site, leading to a localized and increased drug concentration at the site. This system has several advantages over chemical penetration enhancers. Among them are a sustained drug release, and protection of the active drug from degradation processes. Together, these attributes result in a lower amount of active drug usage and fewer cutaneous side effects.⁵⁸

The formulations of nanocarriers can be classified by their size, structure, chemical properties, composition of materials, and main constituents.⁵⁹ Several types of nanomaterials for topical MTX have been recently reported. Nanocarriers can be divided into several groups: lipid-based nanocarriers, polymer-based nanocarriers, metal-based nanocarriers, and composite materials drug delivery system. Sixteen studies investigated topical MTX using nanotechnology delivery techniques: two with humans, and fourteen using animal-models of psoriasis.^{8,19–21,23–30,32,34–36} In the 2 human studies, the reported clinical efficacy of MTX in liposomes conflicted (Table 2). In the animal models of psoriasis, topical MTX using nanotechnology demonstrated promising results in all studies. Overall, there were no local and systemic side effects.

Topical MTX with Liposomes

Liposomes are lipid-based nanocarriers which are considered safe and non-toxic because of their main constituent, a phospholipid bilayer. They are small, nanosized, spherical-shaped structures in which amphiphilic lipid molecules arrange themselves in a bilayer pattern.⁶⁰ Due to their structure, liposomes can encapsulate and improve the stability of both hydrophilic and hydrophobic drugs at target sites. With their vesicular structure, liposomes act as a biological membrane that has the ability to carry a drug and avoid drug destabilization. Therefore, loading MTX in liposomes can enhance its transdermal drug delivery. A low amount of MTX in a liposome preparation but a high MTX concentration presented to the epidermis may improve psoriatic skin lesions with fewer cutaneous and systemic side effects than are produced by using conventional methods.^{37,60} However, the drawbacks of conventional liposomes have been found to be instability and drug leakage from the vesicles.³⁷ Moreover, some of the liposomes fail to penetrate deep into the epidermis, remaining instead in the upper part of the stratum corneum.⁶¹ To overcome these challenges, niosomes (1st generation), transfersomes (2nd generation) and ethosomes (3rd generation) have been developed to increase the skin penetration of the active drug.⁶²

Although having a bilayered structure similar to liposomes, niosomes are mainly composed of non-ionic surfactants (non-ionic, surfactant-based vesicles). Due to their biodegradable and non-toxic nature, niosomes are now widely studied as an alternative to conventional liposomes because of their greater stability, higher drug entrapment efficiency and lower cost.^{25,63} Lakashmi et al reported the method to encapsulate MTX into niosomes and then incorporate the structure within chitosan gel. This gel promotes the absorption effect of MTX in niosomes by increasing the adhesive effect between the formulation and the stratum corneum. Lakashmi et al performed an RCT study of 0.25% niosomal MTX, incorporated into chitosan gel, comparing it with an 0.25% marketed MTX gel and a placebo in 30 patients with plaque-type psoriasis. The 0.25% niosomal MTX gel was significantly more efficacious than the 0.25% marketed MTX gel and the placebo.²⁵ In 2021, Yang et al developed MTX-nicotinamide niosomes based on ceramide (cerosomes).³⁶ As nicotinamide has an anti-inflammatory property, this substance was proposed to synergize the efficacy of MTX. They tested this formulation in imiquimod induced psoriasis mouse model and compared the efficacy with oral MTX and other topical MTX/nicotinamide formulations. They found that Psoriasis Area and Severity Index (PASI) score and epidermal thickness after applying MTX-nicotinamide cerosomes daily for 7 days were significantly lower than other treatment groups.

Transfersomes, also termed deformable liposomes, are elastic lipid vesicle carriers which are composed of phospholipids and an edge activator-like surfactant that is a membrane-softening agent.⁶¹ When transfersomes reach the skin pores, they are capable of deforming their membranes and squeezing through the pores spontaneously. This ability stems from the elastic nature of transfersomes.⁶⁴ When compared with conventional liposomes, transfersomes demonstrated an increased drug penetration depth and improved drug efficacy and stability.³⁰ Vanaja et al compared the effects of an 0.25% ultra-deformable liposomal MTX gel with those of a 1% plain MTX gel in 25 patients with psoriasis.³⁰ The 2 gels demonstrated comparable efficacy. However, they concluded that the ultra-deformable liposomes demonstrated an improved topical drug delivery of MTX because a lower MTX concentration was used in the liposomes.³⁰ Bahramizadeh et al developed MTX-entrapped deformable liposomes containing oleic acid; their efficacy was investigated in an imiquimod-induced mouse model of psoriasis. It was found that treatment with 0.05% MTX liposomes significantly reduced the severity of psoriasis. A reduction in epidermal thickness, as determined by histopathology, was significantly achieved with both 0.05% and 0.1% MTX liposomes.²¹

Ethosomes are elastic lipid vesicle carriers which are composed of phospholipids and ethanol, resulting in a high deformability and elasticity of the vesicle carriers. They can pass through the intracellular space of the skin, and they have a high drug-entrapment ability.⁶¹ Moreover, ethanol disrupts the lipid bilayer of the stratum corneum, resulting in high drug penetration to deep skin layers.⁶⁰ Chandra et al studied an ethosomal gel of 0.25% MTX incorporated with 2% salicylic acid in a mouse model of psoriasis (n = 12). The clinical and histopathological skin severities were reduced more in the MTX ethosomal group than in the blank gel group.²³

Topical MTX with Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are comprised of biodegradable lipids, and a surfactant which has a solid lipid core and is able to encapsulate both hydrophilic and hydrophobic drugs. Nanostructured lipid carriers (NLCs) are a new generation of solid lipid nanoparticles to overcome the limitations of SLNs, which are limited drug loading capacity, drug leakage and stability. NLCs are colloidal carriers that are developed from a blend of solid and liquid lipids to form a drug-incorporated matrix.^{65,66} Unlike solid lipid nanoparticles, NLCs have defects in their crystal lattice that provide more space to load drug encapsulations. The advantages of NLCs are their high drug-loading capacity, minimal drug leakage and controlled drug-release rate. Moreover, they can form a thin film overlying the skin, thereby increasing skin hydration.^{19,59,67} Two mouse models of psoriasis revealed clinical and histological benefits of MTX-NLC.^{19,20} The work by Avasaththi et al established that an MTX-NLC nanogel has a superior efficacy to an MTX gel formulation.²⁰ Agrawal et al compared the anti-psoriatic efficacy of MTX-NLC with that of conventional MTX in carbopol gel. The MTX-NLC group achieved a significant reduction in histological severity and inflammatory-cytokine levels than the MTX in carbopol gel. Nevertheless, the improvement in the clinical severity of the MTX-NLC group was comparable to that achieved by the MTX in carbopol gel.¹⁹

Topical MTX with Polymeric Nanoparticles

Polymeric nanocarriers can be developed from natural, semi-synthetic or synthetic polymers.⁵⁸ Many types of polymeric carriers are used for transdermal drug delivery, for example, polymeric micelles, dendrimers, nanocapsules and nanogels.⁶⁸ Polymeric nanogels are three-dimensional hydrogel materials formed by entangled networks of polymeric particles that can trap a large amount of water molecules within the networks. In addition, they have a relatively high drug encapsulation capacity and stability. Polymeric nanogels have shown promising results as a good candidate as a drug nanocarrier.⁶⁹ Panonumal et al developed an MTX-loaded nanogel of chitin (MCNG), which is a natural biodegradable nontoxic polymer. Two MCNG formulations (100 and 150 $\mu\text{g}/\text{cm}^2$) were applied daily for 3 weeks in an imiquimod-induced mouse model for psoriasis. Comparisons were made between 150 $\mu\text{g}/\text{cm}^2$ of conventional MTX in carbopol gel, carbopol gel, control chitin nanogel and a positive control. The results showed that 150 $\mu\text{g}/\text{cm}^2$ MCNG was superior to 100 $\mu\text{g}/\text{cm}^2$ MCNG as well as to 150 $\mu\text{g}/\text{cm}^2$ conventional MTX carbopol gel. The remaining groups were less efficacious than those 3 groups. Moreover, the MCNG-treated group at both MTX doses exhibited less features of histopathological findings of psoriasis than the other groups. No systemic or local adverse effects were reported for MCNG.²⁸ Asad et al developed MTX based nanoparticle-loaded chitosan hydrogel and tested in an imiquimod induced psoriatic mouse model for 10 consecutive days.³² Their formulation was compared with free MTX hydrogel and marketed cream. They found that PASI score was decreased in all of these three groups, but a mark decreased was observed in MTX based nanoparticle-loaded chitosan hydrogel. TNF- α and IL-6 were mostly reduced by MTX based nanoparticle-loaded chitosan hydrogel groups, compared to other treatments.

Topical MTX with Micro-Emulsion and Nano-Emulsion

Micro-emulsion and nano-emulsion are both colloidal dispersion systems. They can be defined as the nanometric dispersion of one liquid phase to another insoluble liquid phase.⁷⁰ They have many similarities and differences in terms of their composition and stabilities. Micro-emulsions are thermodynamically stable colloidal dispersions composed of oil, water and a surfactant.^{66,71,72} Micro-emulsions have hydrophilic and lipophilic domains that react with lipids on the skin. This results in a modification of the intercellular space of the stratum corneum, thereby permitting drug transportation.^{8,73} The dispersed domain sizes are usually between 10 to 50 nm.⁷⁴ Amarji et al compared an 0.25% MTX-loaded micro-emulsion in poloxamer gel with an 0.1% topical dexamethasone and a poloxamer gel (placebo).⁸ Although the MTX-loaded micro-emulsion in poloxamer gel improved clinical psoriasis skin from the third day onwards, a faster onset and higher efficacy was achieved with the topical dexamethasone.⁸

Nano-emulsions resemble micro-emulsions in that both are dispersions of nano-sized particles, but they are thermodynamically unstable. The oil droplet containing the active drug is stabilized by an emulsifier and acts as a drug carrier with the characteristics of lipophilic and solid spheres. Another difference between micro- and nano-emulsions is that the former can develop spontaneously, whereas the latter is obtained by mechanical force.⁷⁴ Rajitha et al developed an MTX-nano-emulsion gel in a chaulmoogra-oil base and demonstrated its anti-psoriatic efficacy in animal models. Chaulmoogra oil is a traditional medicine containing many bioactive fatty acids that have anti-inflammatory properties. A daily application of MTX-nano-emulsion gel in a chaulmoogra-oil base for a month (cumulative MTX dose = 25 mg/week) produced a better clinical improvement than oral MTX (15 mg/week for a month).²⁹ Rashid et al developed olive oil-based MTX nanoemulsion gel (MTX NEG) and tested the efficacy in imiquimod-induced mouse model of psoriasis. MTX NEG was applied daily for 28 days and its efficacy was compared with MTX plain gel, olive oil and oral MTX.³⁴ MTX NEG and oral MTX demonstrated the highest percentage of PASI score reduction at the end of study (94.9% and 91.7%, respectively). While MTX plain gel and olive oil showed less improvement in PASI score reduction (61.3%, and 45.9%, respectively).

Topical MTX with Metal Nanoparticles

Metallic nanocarriers have gained attention in biomedical applications because of their small size, relatively high surface area to volume ratio, ease of preparation, and versatile surface modifications. Examples of these nanocarriers are gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs).⁵⁹ AuNPs are very small (1–100 nm), inert and low toxicity materials which can easily penetrate cells and deliver active drugs. Moreover, AuNPs have an immunomodulatory effect that can reduce the production of proinflammatory cytokines such as tumour necrosis factor- α and interleukin-6, both of

which are related to the pathogenesis of psoriasis.⁷⁵ To date, the anti-psoriatic benefits of AuNP have only been demonstrated in animal studies.

Fratoddi et al developed gold nanoparticles that were functionalized with sodium 3-mercaptopropane sulfonate (AuNPs-3MPS) and loaded with MTX. Although the nanoparticle was applied daily for only 1–2 days, it reduced clinical scaling and erythema more significantly than AuNPs-3MPS alone.²⁴ Özcan et al also compared the efficacy of MTX coupled with a gold nanoparticle (MTX-GNP) gel (MTX 12.5 mg/kg) with the effects of an MTX gel (MTX 12.5 mg/kg), a GNP gel and a carbopol 980 carrier. The MTX-GNPs showed the significantly highest reduction in ear inflammations of all the groups. Moreover, MTX-GNPs have demonstrated a better histopathological improvement than the topical calcipotriol-betamethasone.⁷⁵

Topical MTX with Nanocomposite Hydrogels

Supramolecular hydrogels are a novel class of three-dimensional hydrophilic polymers cross-linked by non-covalent bonds. They show high physical stability and drug-loading capacity.⁶⁷ Limon et al developed nanostructure supramolecular hydrogels of MTX and compared their efficacy with that of a topical MTX sodium salt solution at the same concentration in a mouse model of psoriasis.²⁶ The nanostructured supramolecular hydrogels of MTX showed a comparable treatment efficacy to MTX solution, but the hydrogels induced a swifter response. The faster onset of action may be due to an enhancing of the drug permeation or to a prolonging of the drug retention by the supramolecular gel.²⁶ In 2022, Xu et al developed MTX-Zinc oxide/Ag (ZA) embellished with nanomicelles (NMs) and further embedded with carbopol(Car); (Car@NMs@MTX-ZA hydrogels). This formulation was applied on skin of the psoriatic-induced mouse model daily for 6 days. The efficacy was compared with Car@NMs@MTX hydrogel, Car@NMs@ZA hydrogel, Car@MTX hydrogel, Car@ZA hydrogel, Car@MTX-ZA hydrogel, zinc oxide and blank carbopol hydrogel.³⁵ They found that Car@NMs@MTX-ZA hydrogels exhibited the best effect in PASI score reduction, improvement of psoriatic histopathological changes and suppression of several pro-inflammatory cytokines.

Topical MTX with Protein Transduction Domains or Cell-Penetrating Peptides

Protein transduction domains (PTDs) are small cationic molecules which consist of 30 or fewer amino acids residues. They can transport and deliver drug molecules through cell membranes.⁵⁸ PTDs also have the potential to convey lipid nanoparticles (liposomes and NLC) across the skin layers.⁵⁸ Byamba et al developed PTDs conjugated with MTX, which could be considered as a skin-permeable MTX. One injection of intraperitoneal MTX (35 mg/kg) was compared with 0.1% and 1% skin-permeable MTX daily for 3 days. The anti-psoriatic efficacy (measured by the decrease in the PASI score) of the 1% skin-permeable MTX was better than that achieved with the intraperitoneal MTX.²² While PTD systems have shown good efficacy and favourable safety profiles, the number of human and animal-model studies on psoriasis is very limited.

Topical Methotrexate with Liquid Crystalline System

Liquid crystals are designated as state that is located between solid and liquid state. It has gained attention in drug delivery development as they have the ability to include either lipophilic or hydrophilic drug regardless of drug dimensions.⁷⁶ This system could be able to enhance drug solubility and control drug release rate. Furthermore, liquid crystals are easy to scale up, cheap, and thermodynamically stable.⁷⁷ However, the result of two studies applying MTX-loaded liquid crystalline system on psoriatic-induced animal models was disappointed. Their histopathological results after using these formulations in psoriatic-induced mouse model were not improved and inflammatory cytokine parameters after using these formulations were higher, comparing to the control.^{31,33}

Topical Methotrexate with Physical Enhancers/Laser/Photodynamic Therapy

Seven published studies investigated the use of topical MTX with physical enhancers/laser/photodynamic therapy. Two examined the use of topical MTX with lasers for human psoriasis skin lesions. One investigated the use of topical MTX coupled with photosensitizer in photodynamic therapy in animal models of psoriasis. Three considered topical MTX with

iontophoresis for palmoplantar psoriasis treatment. The seventh study explored the application of topical MTX via microneedle patches with hyaluronic acid in animal models of psoriasis (Table 3).

Topical MTX with Diode Laser

Ali et al conducted an RCT study using 0.25% deformable liposome MTX hydrogel once daily with 650 nm diode laser irradiation 3 times weekly for 12 weeks. The results were compared with those of a plain MTX gel with a similar diode laser, and of a placebo (laser alone), in 30 patients with psoriasis.³⁷ After exposure to visible or ultraviolet light, the deformable liposomes break down and release MTX, with no effect on MTX chemical stability. This expedites or enhances MTX release from deformable liposomes, which leads to a high MTX concentration in the epidermal layer. The investigations by Ali et al revealed that 46.6%, 13.3% and 0% of the patients administered the deformable liposomal MTX gel, plain MTX gel and placebo, respectively, achieved complete clearance of the psoriatic lesions at the end of the 12-week treatment period.³⁷

Topical MTX with Fractional Laser

An ablative fractional laser modifies the stratum corneum by partial removal of the skin surface. It creates microchannels in the skin, enabling delivery of hydrophilic and high molecular weight drugs like MTX.⁷⁸ Drug diffusion is increased not only by the enlargement of the absorption area, but also by the microchannels, which act as a reservoir for drug delivery.⁷⁸ Ramez et al combined the fractional erbium: YAG (yttrium aluminium garnet) laser with a 0.1% nanoparticulated MTX micro-emulsion based on jojoba oil. Intra-individual left-right comparisons were also made of the MTX micro-emulsion with, and without, fractional erbium: YAG assisted delivery. Both sides showed a reduction in thickness, erythema and scale, but the side with fractional erbium: YAG showed a higher significant reduction.⁴¹

Topical MTX with Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment that uses photosensitizing drug along with light to destroy abnormal cells. 5-Aminolevulinic acid (ALA) is the well-known photosensitizing agent that was approved by the Food and Drug Administration to use for PDT treatment.⁷⁹ Wang et al reported the successful usage of chitosan/hyaluronan co-loading with MTX-ALA nanogels plus the irradiation with 635 nm laser.⁴³ They performed their experiment in imiquimod induced mouse model of psoriasis and compared their formulation with oral MTX and other topical MTX or ALA plus irradiation. They found that MTX-ALA nanogels exhibited the best effect in decreasing the PASI score, compared to other treatment groups. Moreover, only MTX-ALA nanogels group can normalize the levels of TNF- α and IL-17A to those of the normal control group. The safety of topical MTX-ALA nanogels was confirmed by the histological analyses in heart, liver, spleen, lung, and kidney of the mouse which was not showing any abnormalities.

Topical MTX with Iontophoresis

Iontophoresis utilises micro-electrical assistance to achieve transdermal drug delivery. A direct electrical current drives ionically charged drugs through the skin. The dose of the delivered drug depends on the total electric charge. Generally, iontophoresis is used to deliver hydrophobic, low-molecular-weight drugs.⁸⁰ However, the ionic structure of MTX is also suitable for the mechanism of iontophoresis.⁴² Two studies and 1 case report, all from India, used a topical MTX solution with iontophoresis for palmoplantar psoriasis treatment.^{38,40,42} Overall, the efficacy of MTX plus iontophoresis was not remarkable. This was probably due to the large MTX molecule-size and the recalcitrant nature of palmoplantar psoriasis.

In 2003, Tiwari et al reported the successful treatment of a palmoplantar psoriasis patient by using a topical MTX disodium solution (10 mg/mL) soaked in gauze, combined with iontophoresis.⁴² Haseena et al conducted an intra-individual comparison study using an MTX solution (50 mg/2 mL) diluted in 50 mL of water soaked in gauze plus iontophoresis.⁴⁰ The side treated with MTX plus iontophoresis showed a statistically significant reduction in palmoplantar-psoriasis severity, compared with the control side.⁴⁰ Andanooru Chandrappa et al conducted a prospective, randomized, unblinded study on 50 palmar psoriasis patients, comparing the efficacy of cotton gauze soaked in MTX solution (15 mg/mL) plus iontophoresis, with the effects of 0.05% clobetasol propionate ointment.³⁸ With its greater number of patients, the research revealed that the efficacy of the MTX solution plus iontophoresis once weekly was comparable with that of a twice daily application of topical clobetasol propionate. However, it should be noted that fewer

milliamperes of iontophoresis were used in the work by Andanooru Chandrappa et al. A considerable number of trivial and self-limiting burn injuries were observed in that study.³⁸

Topical MTX with Microneedle Patches

Microneedle techniques use needles to create micro-pores in the skin prior to the application of a topical drug. This physical technique facilitates drug penetration. The microneedles are made from a variety of materials, and are available in solid or hollow forms. However, drug uptake can be limited once the needles are removed from the skin and the micropores begin to close. Microneedles using hyaluronic acid (HA), or HA-based dissolving microneedles, have been developed to overcome these limitations. HA-based microneedles dissolve upon insertion while simultaneously releasing drug into the skin. This innovation both simplifies the administration of the drug and increases its uptake by the skin.³⁹

Du et al developed an MTX-loaded HA-microneedle patch and conducted the study in an imiquimod-induced mouse model of psoriasis. Firstly, they compared the antipsoriatic efficacy of MTX-loaded HA-microneedle patches at a low MTX dose (6.5 µg), medium MTX dose (13.8 µg) and high MTX dose (30.6 µg). They found that the MTX-loaded HA-microneedle patches improved the clinical, histological and inflammatory outcomes in a dose-dependent manner. Secondly, they compared the efficacy of a medium-dose HA-microneedle patch (13.8 µg of MTX) with that of oral MTX at the same dose (13.8 µg) and at a double dose (27.6 µg of MTX). The medium-dose HA-microneedle patch was superior to the oral MTX of the same dose level. An analysis of the epidermal thicknesses achieved with the medium-dose HA-microneedle patch and with the double dose of oral MTX revealed comparable efficacy levels. Both therapies were significantly superior to oral MTX at the same dose as for the microneedle patch. This indicated that an MTX microneedle patch had a higher antipsoriatic efficacy than oral MTX at the same dose.³⁹

Intralesional MTX

Eleven studies examined the use of intralesional MTX for psoriasis (Table 4).^{15,44–53} One study of its efficacy for psoriasis skin lesions found no significant improvements. By contrast, all 10 studies investigating its efficacy for nail psoriasis demonstrated significant improvements in the nail matrix and nail bed. The most common treatment for the nail psoriasis was a 2.5 mg MTX solution injected at the nail matrix. As psoriasis nails are usually recalcitrant to both conventional topical and systemic treatments, an intralesional MTX injection which gives a high drug concentration to the target nail tissue is an interesting choice. Nevertheless, its side effects—especially pain, subungual hematoma and transient post-injection numbness—may limit its usage.^{44,46,48,53}

There were 3 studies comparing the efficacy of intralesional MTX (25 mg/mL) for nail psoriasis with intralesional triamcinolone acetonide (10 mg/mL).^{48,51,53} Two studies reported the good and comparable efficacy of intralesional methotrexate and triamcinolone acetonide with more stability of the result from MTX group in one study.^{48,53} While Abdelmeniem et al reported that the mean Nail Psoriasis Severity Index (NAPSI) score improvement of intralesional MTX was less than intralesional triamcinolone acetonide and topical 0.005% calcipotriol cream plus 20% urea under occlusion at psoriatic nail.⁵¹

The efficacy of intralesional MTX for nail psoriasis was compared with fractional laser assisted drug delivery in one study.⁵² Fractional carbon dioxide (CO₂) laser plus topical application of 0.1 mL of MTX 25 mg/mL and intralesional MTX (25 mg/mL) were given biweekly for 6 weeks in 28 patients with nail psoriasis. They found that Fractional CO₂ laser plus topical MTX displayed a comparable improvement to intralesional MTX but the laser group was associated with less side effects (pain and subungual hematoma).

Conclusion

Studies related to topical MTX in patients with psoriasis are limited. The efficacy of plain MTX in an aqueous cream or gel and of topical MTX with chemical enhancers do not seem promising due to their difficulty achieving skin penetration and their high risk of skin irritation. Nanoscale-based drug delivery—with and without physical enhancers such as an ablative laser or microneedle patches—are an interesting option. Most nanoscale drug delivery systems have shown good efficacy in animal models of psoriasis. However, data on the use of those techniques in patients with psoriasis are scarce. This review will benefit researchers worldwide who are pursuing the development of the most suitable formations of

topical MTX. Further studies with a larger number of patients are needed to establish the most effective drug delivery system for psoriasis treatment.

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