

Experimental research in topical psoriasis therapy (Review)

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Received January 5, 2021; Accepted February 4, 2021

DOI: 10.3892/etm.2021.10403

Abstract. Psoriasis, one of the most prevalent inflammatory diseases in dermatologic pathology, remains a challenge in regards to the therapeutic approach. Topical therapy for psoriasis is a current trending subject as it implies good compliance for the patient, few adverse systemic reactions and a targeted effect. Numerous substances are now being tested, from natural to synthetic compounds and already known substances in improved formulas such as vesicular systems. The aim of this article was to conduct a literature review regarding the topical therapy of psoriasis in animal models, between June, 27, 2019 and July 9, 2020. For this article, the authors conducted extensive research in PubMed with the following keywords: Psoriasis AND (topical OR local) and (therapy OR treatment) AND (mice OR rats). The main new studied substances included lycopene, sodium butyrate, salvianolic acid B, small interfering RNAs (siRNAs) in ionic liquids, albendazole, phosphodiesterase inhibitors, biomimetic reconstituted high-density lipoprotein nanocarrier gel containing microRNA (miRNA)-210 antisense, thymoquinone in ethosomal vesicle, Sea buckthorn oil (*Hippophae rhamnoides*), nitidine chloride, *Melissa officinalis* spp. *Altissima* extract and [1-(4-chloro-3-nitrobenzenesulfonyl)-1H-indol-3-yl]-methanol (CIM). New formulas of already known anti-psoriasis substances such as: Cyclosporine, methotrexate, calcipotriol, tazarotene, protein kinase p38 and integrin $\alpha 5\beta 1$ as a target, are also reviewed. Recent research in topical psoriasis underlines the importance of animal experimental research in dermatology, providing

a starting point for developing new therapeutic approaches in one of the most frequently diagnosed chronic dermatologic diseases. Vesicular systems are now providing the best vehicle for topical therapy, thus easing the action of the active substances at their target sites.

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1. Introduction

Psoriasis represents a chronic, incurable, immune-mediated disease, being a combination between polygenic predisposition and external triggers (trauma, microorganism, drugs) or internal triggers (stress) (1). Psoriasis is one of the most prevalent dermatological diseases and a continuous challenge in regards to therapeutic approach.

The key in initiating the characteristic lesions of psoriasis is dendritic cell stimulation by Toll-like receptors (TLRs) with interferon (IFN α and IFN β) production, followed by regional ganglia migration and tumor necrosis factor (TNF α , interleukin (IL)-23 and IL-12 production. The latter (IL-23 and IL-12) stimulate LTh17 and LTh1 subtype differentiation. In the steady phase, adaptative immune system is activated with Th-17 cytokine secretion (IL-17, IL-21, IL-22) and dermal proliferation. Therefore, the TNF α /IL-23/Th-17 axis is characteristic for psoriasis vulgaris and psoriatic arthritis (2). Intracellular activated kinases through this way include: Extracellular signal-regulated kinase (ERK), p38 MAPK (mitogen-activated protein kinases), transforming growth factor (TGF)- β -activated kinase 1 (TAK1), I κ B kinase (IKK), and glycogen synthase kinase 3 β (GSK-3 β). These kinases enable nuclear factor (NF)- κ B, AP-1, and C/EBP transcription

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Key words: psoriasis, topical, treatment, mice, imiquimod

of pro-inflammatory cytokines, chemokines, and antimicrobial peptides (3-6).

Currently, along with evolving systemic therapy, biological treatment has revolutionized severe psoriasis management. Topical treatment is especially recommended for localized and moderate forms of psoriasis and aims to decrease the severity of hyperkeratosis (preparations with tar, dioxyanthranol, salicylic acid) and decrease keratinocyte proliferation (topical retinoids, vitamin D3 analogues). Dermatocorticoids are first-line active agents in the topical treatment of psoriasis with important local side effects such as atrophy, hypopigmentation, and superinfections.

The experimental models used to evaluate psoriasis changes in laboratory animals are mainly the imiquimod (IMQ) mouse model, the mouse tail model, and the carrageenan and TPA (12-*O*-tetradecanoylphorbol-13-acetate) inflammation induction models.

The present trend is to discover either new effective or already approved substances conditioned in superior formulas in regards to absorption and efficacy and new mechanisms with anti-psoriasis potential.

2. Research methods

The aim of this article was to conduct a literature review regarding research on the topical therapy of psoriasis in animal models, between June, 27, 2019 and July 9, 2020.

For this article, the authors conducted extensive research in PubMed with the following keywords: Psoriasis AND (topical OR local) AND (therapy OR treatment) with publication dates January 1, 1995 to July 15, 2020 for search 1 and also psoriasis AND (topical OR local) AND (therapy OR treatment) AND (mice OR rats) for search 2.

The first search was made in order to assess the scientific interest in the topic. The second search had the following steps: Introduction of words and limits in PubMed with first step exclusion criteria for articles that did not refer to a potential substance for topical therapy, formulas from traditional medicine that did not specify the active ingredient (7-17). The second step exclusion criterion was if the substance of interest was not administered topically. The search was performed by two authors in the PubMed database and the results were mediated.

The data extracted from each article referred to newly tested substance or known substance with a new pharmaceutical form (dosage, pharmaceutical form, concentration), the experimental model used and the mechanism of action involved.

3. Summary and discussion of the new topical treatment strategies

Interest in topical psoriasis therapy has increased over time. Regarding the number of articles between 1951 and 2020, the first keywords were used (see search 1).

The total number of articles was 6,052 (4,572 between 1995 and 2020) until July 9, 2020. In the last 25 years, the interest has increased with a peak in 2018 and a slight decrease over the last 2 years (Fig. 1). The trendline is at an average of 5 years. In the last year (June 27, 2019 to July 9, 2020),

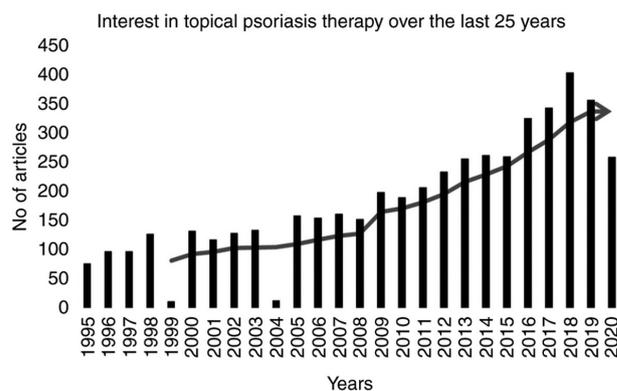


Figure 1. Interest in topical anti-psoriasis therapy over the last 25 years.

41 articles were found and 23 were deemed articles of interest (Fig. 2) and are summarized as follows in Tables I and II.

In a study by Shih *et al* lycopene, a terpenoid carotenoid, was administered orally at a dose of 0.06 and 0.12 mg/kg/day and topically at a dose of 0.06 and 0.12 mg/ml of ointment in the imiquimod (IMQ) model. The results revealed a dose-dependent decrease in the Psoriasis Area Severity Index (PASI), epidermal hyperplasia and cell adhesion on HaCaT cultures stimulated by TNF α , demonstrating the anti-psoriasis effect (18) (Table II).

In a study by Li *et al* graphene oxide in hydrogel was used as a nano-carrier in order to increase the permeability and retention of cyclosporine in tissue. Efficacy evaluation was performed *ex vivo* on goatskin and modified Franz cells (diffusion area 1 cm²) and *in vivo* on rabbits for evaluation of irritant effect and on a TPA model in mice. The results demonstrated an increase in the permeability and tissue retention of cyclosporine while avoiding the effects of systemic administration (19) (Table II).

Mometasone furoate, a widely used corticosteroid in dermatological pathology with a certain anti-psoriasis effect, has recently been conditioned as an apasomal gel used topically against psoriasis. In a study by Shinde *et al* compared to the available cream that has a 5-h release, the release of the new formula took place over 24 h (20) (Table II).

Short-chain fatty acids in the colon induce regulatory T cell (Treg) generation. Schwarz and colleagues studied the effect of topically applied sodium butyrate using the IMQ model. The results revealed a IL-17 decrease and IL-10 and Foxp3 increased transcription. The data thus demonstrated that a Treg imbalance occurs in psoriasis that can be ameliorated by sodium butyrate (21) (Table II).

In a study by Guo *et al* salvianolic acid B with anti-inflammatory, antioxidant and antitumoral properties was investigated using the IMQ model for psoriasis. Salvianolic acid B in microemulsion was shown to reduce acanthosis, epidermal proliferation, inhibit cytokine IL-23/IL-17 axis and increase skin hydration, having anti-psoriasis potential (22) (Table II).

Small interfering RNAs (siRNAs) can be used to suppress gene-specific alleles for various diseases such as psoriasis, lupus, hyperhidrosis, and neoplasms. For this purpose, the topical administration in the form of ionic liquids capable of forming non-covalent bonds with siRNA and

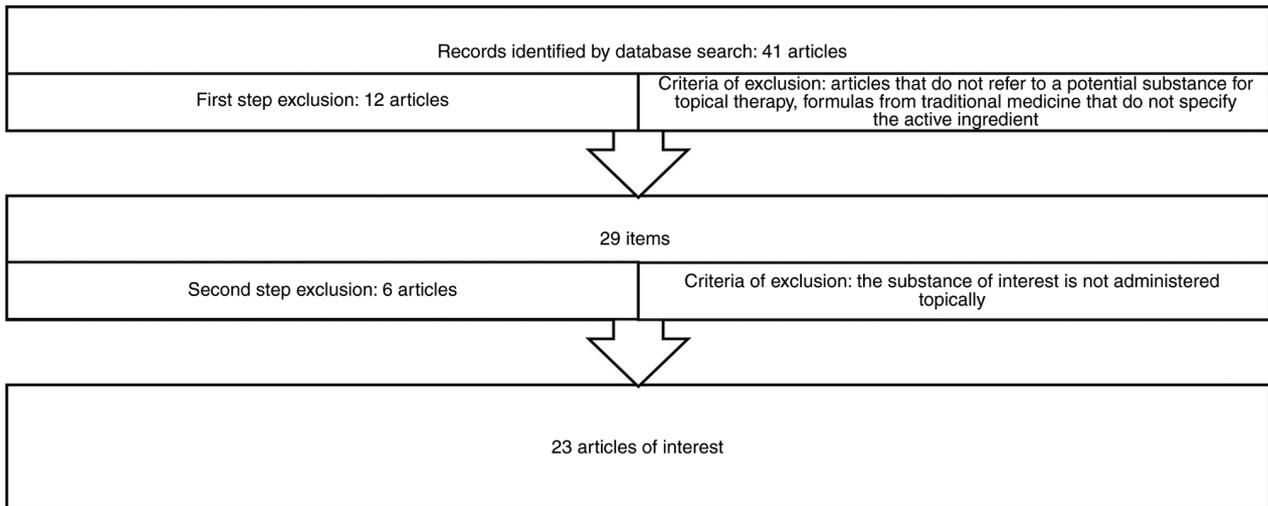


Figure 2. Criteria of inclusion/exclusion used in regards to the literature studies.

achieving adequate absorption was attempted in a study by Dharamdasani *et al* Hydrophobic cations were used to bind RNA and ionic liquid of choline-geranic acid to increase permeability. The experiments were performed *in vitro* on pig skin and *in vivo* on SKH-1E mice (23) (Table II).

Phosphodiesterase, an intracellular enzyme that hydrolyzes cGMP, is involved in multiple physiological processes. DC591017, a PDE4 (phosphodiesterase 4) inhibitor, was studied by Li *et al in vivo* and *in vitro* for its anti-psoriasis effect, and was found to decrease the inflammatory infiltrate and epidermal thickness. The IMQ and carrageenan models were used for this purpose (24) (Table II).

In a study by Di Fusco *et al* albendazole, an anthelmintic drug, was investigated in topical administrations using the experimental model of imiquimod in mice, with decreased keratinocyte proliferation, reduced keratin (K)6/K16 expression, reversibly inhibiting cell cycle by S-phase cell accumulation. Using this model, albendazole was shown to inhibit the protein kinase receptor (PKR), increase eukaryotic initiation factor 2 (eIF2 α) phosphorylation and reduce CDC25A expression thus demonstrating an anti-psoriasis effect (25) (Table II).

Calcipotriol (CPT), a first-line topical drug in psoriasis vulgaris, was tested as an improved formula in regards to transdermal administration, avoiding adverse skin reactions due to loss of hydration in the epidermis. *Bacillus amyloliquefaciens* (named ZWJ strain) was identified as a producer of high-emulsification exopolysaccharides (EPS). The effect of the formula was tested by animal experiments, providing a scientific basis for future usage (26) (Table II).

In a study by Lee *et al* CO₂ fractional laser was used to increase the permeability of the substance in the psoriatic plaque. A 64% decrease in IL-6 expression in the psoriatic plaque was demonstrated with topical application of IL-6 siRNA using the imiquimod psoriasis induction model. The conventional route of siRNA delivery for dermatological treatment is injection, with adverse reactions such as pain and difficult administration (27) (Table II).

After Feng *et al* (28) demonstrated in a previous study the involvement of microRNAs (miRNAs/miRs) in the

pathogenesis of psoriasis, an anti-psoriasis effect was obtained after topical administration of antisense miRNA-210 in a reconstituted high-density lipoprotein nano-transporter gel. The formula decreased the level of miRNA-210 with reduction of erythema, scales, acanthosis, dermal infiltrate and of IL-17A, using the IMQ model (28) (Table II).

Thymoquinone, a liposoluble benzoquinone is the major substance in the volatile oil of *Nigella sativa* and has an anti-psoriasis effect. However, being practically insoluble in water and photosensitive, topical application in conventional formulas does not provide benefits. Thus, research using thymoquinone-loaded ethosomal vesicles in hydrogels was tested using the tail model for psoriasis. The study showed promising results in terms of anti-psoriasis effect of thymoquinone (29) (Table II).

Sea buckthorn oil extracted from *Hippophae rhamnoides*, which contains 16 types of monounsaturated and polyunsaturated fatty acids, was tested for its anti-psoriasis effect *in vitro* using human THP-1 cells, *in vivo* in systemic and topical administration in the model of paw edema in mice with carrageenan and on a CD-1 model of psoriasis in mice with TPA. The results of these studies were the reduction of reactive nitrogen species and NF- κ B expression, depending on the concentration of the substance under investigation, along with pro-inflammatory cytokines IL-1 β , IL-6, inflammation and epidermal thickness reduction (30) (Table II).

Nitidine is a natural alkaloid extracted from *Zanthoxylum nitidum* (Roxb), with anti-proliferative properties using the ERK signaling pathway with antitumor potential in colorectal cancer (31) and a potent inhibitor of HaCaT keratinocyte proliferation *in vitro*, with decreased DNA synthesis, decrease in Ki67, cyclin A and D1 levels and with p53 protein increase. On experimental models with imiquimod/TPA topical application, epidermal thickness, edema and pro-inflammatory cytokine levels were decreased (32) (Table II).

Indole-3-carbinol (I3C) is a natural compound with anti-neoplastic effect. [1-(4-Chloro-3-nitrobenzenesulfonyl)-1H-indol-3-yl]-methanol is a new I3C derivative. Upon topical application in the IMQ model, the latter compound decreased hyperplasia and inflammation, with suppression

Table I. New substances and improved formulas in topical psoriasis treatment.

New topical substances tested	Substances in superior topical formulas/new mechanisms
Lycopene	Cyclosporine-loaded Pluronic® F127 stabilized reduced graphene oxide hydrogel
Sodium butyrate	Mometasone furoate-loaded aspasomal gel
Salvianolic acid B	Exopolysaccharides/calcipotriol emulsion
Small interfering RNAs (siRNAs) in ionic liquids	IL-6 siRNA-fractional CO ₂ laser
Albendazole	Topical gel of methotrexate (0.25%) incorporated ethosomes and salicylic acid (2%)
Phosphodiesterase 4 inhibitors	Topical methotrexate-entrapped deformable liposome
Biomimetic reconstituted high-density lipoprotein (rHDL) nanocarrier gel containing miR-210 antisense (NG-anti-miR-210)	p38 protein kinase as a target with BIRB796 as inhibitor
Timoquinone in ethosomal vesicle	Tazarotene enriched with 1% cineole
Sea buckthorn oil (<i>Hippophae rhamnoides</i>)	Celastrole in niosome gel
Nitidine chloride	C16 with antagonistic effect against integrin $\alpha 5\beta 1$
<i>Melissa officinalis</i> spp. <i>Altissima</i> extract [1-(4-Chloro-3-nitrobenzenesulfonyl)-1H-indol-3-yl]-methanol (CIM)	
Manganese porphyrin	

of cytokines specific to the MAPK, NF- κ B and AP-1 pathways (33) (Table II).

In a study by Chandra *et al* the combination of methotrexate with salicylic acid in ethosomal gel with a particle size of 376.04 ± 3.47 nm was tested in the IMQ model and then compared to methotrexate solution. The results showed a 43% retention study for the gel compared to 13% for the solution, with decreased PASI and normalization of psoriatic plaques (34) (Table II).

In a study by Dimitris *et al* *Melissa officinalis* spp. *Altissima* extract (lemon balm) was tested using the IMQ model. Chemical analysis was performed to detect active metabolites. From the dichloromethane extract, seven triterpenes were isolated, i.e. ursolic acid, 2 α -hydroxy-ursolic acid, pomolic acid, 3 β -stearoxy-urs-12-ene, oleanolic acid, noropacursane and campesterol. The methanol extract yielded two phenolic acids (rosmarinic acid and methyl rosmarinate), which seem to be the major compounds of the total methanol extract. In addition, from the decoction, three phenolic acids were isolated: Caffeic acid, 3-(3,4-dihydroxyphenyl) lactic acid and rosmarinic acid. Extracts with dichloromethane and methanol and decoction were used. Triterpene derivatives of the dichloromethane extract were shown to be responsible for the anti-psoriasis effect. The polyphenols in the decoction were responsible for the strong antioxidant effect, with the strongest anti-psoriasis effect (35) (Table II).

Topical methotrexate embedded in deformable liposomes with phosphatidylcholine and oleic acid in concentrations of 0.05 and 0.1% demonstrated significant anti-psoriasis effect in the model of psoriasis with IMQ (36), without significant toxicity as in systemically administrated methotrexate (37-39). Methotrexate has low skin permeability due to high molecular

weight and hydrophobicity, thus the liposomal form is optimal for increasing bioavailability (Table II).

The involvement of p38 protein kinase in the pathogenesis of psoriasis was investigated using the IMQ model. Anisomycin, a murine p38 activator with psoriasis-producing effect and BIRB796, a p38 inhibitor with anti-psoriasis effect, were used (40) (Table II).

Tazarotene is a synthetic topical retinoid used in the treatment of psoriasis but with a lipophilic structure causing irritating side effects. Recent *in vitro* and *ex vivo* research conducted by Elmowafy *et al* (41) regarding nanovesicles enriched with 1% cineole recorded a significant loading of tazarotene with a total of 81.51% in all epidermal layers. Statistically significant results were obtained in terms of PASI score, dermoscopic appearance, anti-psoriasis effect compared to the commercial reference product used (41).

MnTE-2-PyP (BMX-010) (manganese porphyrin) in topical applications is a new anti-psoriatic agent with anti-pruritic effect in nonspecific idiopathic prurigo and atopic dermatitis. Phase I study in 64 patients did not show any significant adverse reactions. The only toxic adverse reaction to maximum concentration in mice was reversible hypertension (42).

Celastrole, a triterpenoid extracted from *Tripterygium*, was developed in a new therapeutic formula, respectively in 147-nm niosomes. Results revealed erythema and scaly relief in the IMQ psoriasis model, with decreased IL-22, IL-23 and IL-17 levels, with an *in vivo* demonstrated increase in skin absorption (43) (Table II).

Integrin $\alpha 5\beta 1$, as a fibronectin receptor, is expressed in excess in the non-lesional epidermis of psoriasis. In order to investigate whether this integrin is a potential target in psoriasis treatment, an antagonist ligand peptide called C16, was

Table II. New tested substances in experimental model research.

Authors	Tested substance	Experimental model	Parameters	Outcome	(Refs.)
Shih <i>et al</i>	Lycopene (0.06, 0.12 mg/ml) ointment	-IMQ model, C57BL/6 male mice of 6-8 weeks -IMQ, 62.5 mg/cm ² , 7 days	-PASI -Epidermal hyperplasia (H&E) -TNF α stimulated HaCaT cultures	-PASI statistically relevant decrease (P<0.05) -Superior effect for topical in decreasing hyperplasia (P<0.05) -ICAM-1 and VCAM-1 cellular adhesion inhibition	(18)
Li <i>et al</i>	Cyclosporine-loaded Pluronic® F127 stabilized reduced graphene oxide hydrogel (C-P-rGO-500)	- <i>Ex-vivo</i> : Goat skin, modified Franz cell - <i>In-vivo</i> : Skin irritation study, TPA model, 2.5 μ g TPA in 5 μ l ethanol, 10 days	-Cyclosporine retention analysis (μ g/g tissue) in goat skin -Sign of irritation (erythema) -Ear thickness	-Cyclosporine trapped/retained in the skin layer C-P-rGO-100, C-P-rGO-500, and C-P-rGO-1000 hydrogels, 29.7 \pm 3.4, 40.7 \pm 2.5, and 28.49 \pm 1.2%, respectively. -No irritation in TPA model for C-P-rGO-500 -C-P-rGO-500 hydrogel demonstrated a maximum decrease in ear thickness when compared with the positive control group; no significant difference (P>0.01) was observed when compared with the betamethasone cream (except day 3)	(19)
Shinde <i>et al</i>	Mometasone furoate-loaded aspasomal gel	-Wistar rats - <i>In-vitro</i> drug release study by using dialysis membrane and goat skin Characterization of vesicular system	-Rat's skin was observed for any kind of redness or inflammation visually -Characterization of vesicular system	- <i>In-vivo</i> study revealed no irritation or inflammation -Sustained release (24 h) compared to the marketed cream (5 h) -Entrapment efficiency (74.72 \pm 1.8), vesicle size (282.9 \pm 1.7), polydispersity index (0.2), zeta potential (-20.2 mV) with spherical shape	(20)
Schwarz <i>et al</i>	Sodium butyrate	-IMQ model, 62.5 mg, 10 days -Eight to nine-week-old female C57BL/6J mice	-Skin thickness -Ear swelling -Histones were isolated from Treg from 3 controls and 3 psoriatic patients	-Back skin thickness (P=8.4x 10 ⁻⁵ vs. IMQ) -Response on ear swelling (P=9.3x10 ⁻⁵ vs. IMQ) reduced imiquimod-induced inflammation and downregulated IL-17 and	(21)

Table II. Continued.

Authors	Tested substance	Experimental model	Parameters	Outcome	(Refs.)
Guo <i>et al</i>	Salvianolic acid/formulation A Composition O:S:W=1:6:3, droplet size (nm) 696.2±188.3, size distribution (PI) 0.435±0.004 Zeta potential (mV), 14.95±0.64 Viscosity (cP) 3112.3±5.8 Electronic conductivity ($\mu\text{sec/cm}$), 24.15±0.07	-IMQ model 62.5 mg, 6 days, BALB/c mice of 6-8 weeks -Skin deposition study	-Barrier function -Cytokine expression -Histology assessment -Disease severity (erythema, scale, induration)	induced IL-10 and FOXP3 transcripts -Sodium butyrate enhances histone acetylation in Treg and corrects cytokine disbalance in psoriatic skin -Sal. B extraction recovery rate from whole skin was 91.5±11.6% at a Sal. B concentration of 0.1 $\mu\text{g/ml}$ in skin deposition study -Sal. B/formulation A group (13.94±7.04 AU) showed higher skin hydration values than that of the control group (3.84±1.60 AU) and DXM (6.10±4.03 AU) groups on day 6 (P<0.05) -IL-17A, IL-17F, IL-22, IL-23 inhibition (all P<0.05), but not IL-17C (P>0.05) and TNF- α (P>0.05)	(22)
Dharamdasani <i>et al</i>	siRNA (small interfering RNA) in CAGE-siRNA, BDOA, BDOA-siRNA, CAGE-BDOA- siRNA formulation 25 $\mu\text{l/day}$	- <i>In vivo</i> : Female SKH-1E hairless mice of 6-8 weeks - <i>In vitro</i> : Skin transport quantification using porcine skin	-FTIR studies -ELISA -RT-PCR	-CAGE and BDOA mediate synergistically siRNA transport (CAGE is more efficient in epidermic and dermic penetration with BDOA mediating intracellular transport)	(23)
Li <i>et al</i>	DC591017 5 mg/kg orally for mice and 50 mg/kg for rats in carrageenan model 2% ointment in IMQ model	-IMQ model-7 days, BALB/c 6-8 weeks old female mice -Carrageenan-induced acute inflammation in murine air pouches and rat paws (C57BL/6 male mice and Sprague Dawley 6-8 male rats) -Murine macrophage cell line RAW264.7 cells	-PASI -Cytokines measurement by Luminex and ELISA assay	-Administration of DC591017 diminished the number of leukocytes (P<0.001) and inhibited TNF- α production in the air pouches (P<0.01). -Topical application of DC591017 ointment significantly attenuated the clinical symptoms and reduced the cumulative severity scores of back skin inflammation since day 1 to the end point (erythema, scale, thickness; P<0.001) -Reduced TNF- α , IFN- γ , IL-2, IL-6, IL-23, IL-27, and IL-9 levels (P<0.05) and increased the production of IL-10 in serum (P<0.05)	(24)

Table II. Continued.

Authors	Tested substance	Experimental model	Parameters	Outcome	(Refs.)
Di Fusco <i>et al</i>	Albendazole (30 µg/mouse) resuspended in 100 µl of propylene glycol	-IMQ model; C57b/6 mice 62.5 mg/day, 4 days -Cell cultures	-Epidermal thickness -Keratin (K)6 and K16 expression (immunohistochemistry and western blotting) -Cell cycle and proliferation, keratins and cell cycle-associated factors	-Reduced epidermal thickness, decreased number of proliferating keratinocytes and K6/K16 expression with IL-6, TNF-α, IL-1β, IL-17A, IL-36, CCL17, CXCL1, CXCL2 and CXCL5 inhibition -In IMQ-treated mice, albendazole activated PKR, enhanced eIF2α phosphorylation and reduced CDC25A expression -Downregulation of CDC25A, a phosphatase regulating progression of cell cycle through S-phase, and PKR-dependent hyper-phosphorylation of eIF2α, an inhibitor of CDC25 translation	(25)
Song <i>et al</i>	Exopolysaccharides/calcipotriol emulsion	-IMQ model, 8 days	-PASI score -H&E staining images -Spleen size -Evaluation of skin irritation	-Reduced PASI score (better than that of the free CPT and the positive control group; P<0.01) -The order of spleen size of each group was as follows: Model group spleen > positive control group > free CPT > EPS/CPT emulsion > normal group -Reduced IL-6 level in blood serum (P<0.05)	(26)
Lee <i>et al</i>	IL-6 siRNA-fractional CO2 laser	-IMQ model	-H&E-stained histology -Cytokine expression measurement	-EPS/CPT emulsion is less irritating than the control Daivonex (P<0.05) -Severity of hyperplasia and scaling IMQ ≥ IMQ+siRNA > IMQ+siRNA ⁺ laser > untreated healthy control -Reduced epidermal thickness (P<0.05) -Reduced cytokine expression IL-6 (P<0.001) -Knockdown of siRNA with a 64% inhibition	(27)

Table II. Continued.

Authors	Tested substance	Experimental model	Parameters	Outcome	(Refs.)
Feng <i>et al</i>	Biomimetic reconstituted high-density lipoprotein (rHDL) nanocarrier gel containing miR-210 (microRNA) antisense (NG-anti-miR-210)	-IMQ model	H&E-stained histology	-Amelioration of erythema, scales, acanthosis and dermal-inflammatory cell infiltration -Decreased proportion of T-helper (Th)1 and Th17 cells in dermal and splenic cells	(28)
Negi <i>et al</i>	TQ suspension (20 mg/kg), NS extract (20 mg/kg), TQ-loaded EV gel (20 mg/kg) TQEV4 having high entrapment efficiency (79.52%), optimum particle size (477.6 nm) and low sedimentation volume (0.1 ml)	-Tail model for psoriasis, 14 days, Albino mice aged between four to 6 weeks	-Induced orthokeratosis (OK) -Presence of the granular layer -Drug activity	-OK-TQ loaded EV gel (55.23 ± 2.05%) > TQ suspension (51.73.2±2.15%) > Tazarotene (51.17±2.03%) > <i>Nigella sativa</i> extract (50.56±3.01%). Drug activity TQ loaded EV gel (25±2.35%) > Tazarotene (19.2±1.05%) > TQ suspension (17.1 ± 1.03%) > <i>Nigella sativa</i> extract (13±1.25%); effect of TQ-loaded EV gel P<0.001 vs. TQ suspension; P<0.001 vs. <i>Nigella sativa</i> extract and; P<0.001 vs. Tazarotene, respectively	(29)
Balkrishna <i>et al</i>	SBKT [100 mg/kg p.o. + 40 µl/paw topical application (T.A.)] or INDO at 10 mg/kg (p.o.), 1 h before carrageenan challenge SBKT (at 100 mg/kg p.o. + 20 µl T.A. and 200 mg/kg p.o. + 20 µl T.A.) or DEXA (0.2 mg/ear T.A.)	-Carrageenan model, Wistar rats injection of λ-Carrageenan (0.1 ml of 1% solution in normal saline) into the plantar side of the left hind paw -TPA model 12-O tetradecanoyl phorbol 13-acetate (TPA) 20 µl of TPA solution (2.5 µg/ear of TPA in acetone) was applied topically on the right ear of CD-1 mice	-The anti-inflammatory activity: Paw edema and paw volume -Ear edema	-Significant reduction of absolute paw volume (P<0.001) and paw edema (P<0.001) -Percent inhibition (at D-10) in the ear edema of DEXA and SBKT 100 and 200 mg/kg (70.05±6.25, 34.05±7.65 and 30.45±8.90%, respectively)	(30)
Yang <i>et al</i>	Nitidine chloride	-TPA, 8 days nitidine chloride 1.5 µg, 11 days -IMQ model 62.5 mg/day, BALB/c mice, 8 days, nitidine chloride (1.5 µg), 11 days	-H&E staining -Cytokine detection	-Nitidine chloride reduced the TPA-induced increases in ear weight and thickness (P<0.0001) -Nitidine chloride treatment significantly reduced the scales and erythema on the areas applied (P<0.0001 vs. IMQ-treated mice) -Decreased cytokine level TNFα, IL-17A, IL-22 (P<0.0001)	(32)

Table II. Continued.

Authors	Tested substance	Experimental model	Parameters	Outcome	(Refs.)
Weng <i>et al</i>	[1-(4-Chloro-3-nitrobenzenesulfonyl)-1H-indol-3-yl]-methanol (CIM)	-IMQ model 62.5 mg/day BALB/c mice, 5 days	-PASI -Epidermal thickness -TEWL -Cytokine detection	-PASI reduction (P<0.001) -Reduced epidermal thickness (53.0 μm compared to 128.4 μm for the vehicle) (P<0.001) -Reduced TEWL (from 48.5 to 37.0 g/m ² /h) (P<0.001) -Decreased cytokine expression possibly threw MAPK, NF-κB, AP-1 inhibition	(33)
Chandra <i>et al</i>	Topical gel of methotrexate (0.25%) incorporated ethosomes and salicylic acid (2%)	-IMQ 62.5 mg/zi, 10 days, 6-8 weeks aged mice	-PASI -H&E staining -Skin retention study	-PASI score reduction (from 4 to 1) -Epidermal thickness reduction -The total amount of drug release from the optimized formulation was 69.14% (retention plus permeation).	(34)
Dimitris <i>et al</i>	<i>M. officinalis</i> ssp. <i>Altrissima</i>	-Male BALB/c mice (6-9 weeks of age, 20-25 g), 62.5mg IMQ daily (5%) plus acetic acid (2%) to the shaved area, 5 days in order to induce severe psoriasis	-PASI score -H&E staining -TEWL evaluation	-Decreased skin thickness (P<0.005) and scaling (P<0.05) for dichloromethane extract and decoction of <i>M. officinalis</i> ssp. <i>Altrissima</i> ; methanol extract enhanced both parameters -Less marked cellular infiltration, parakeratosis and Munro absence observed in mice treated with dichloromethane extract -Reduced psoriasis histopathologic score (PHS) for decoction and dichloromethane (P<0.005) vs. control group -The increase of TEWL significantly lower (P<0.05) for the mice treated with decoction	(35)
Bahramizadeh <i>et al</i>	Topical methotrexate-entrapped deformable liposome	-Female BALB/c mice 8-11 weeks old, IMQ 5%, 11 days	-PASI score -Permeability and retention studies -Pathological studies on the organs	-Significant reduction (P<0.05) in the groups receiving liposomal-MTX -Reduced inflammation (P<0.05) -No lesion in the livers, kidneys and lungs at the end of the study	(36)

Table II. Continued.

Authors	Tested substance	Experimental model	Parameters	Outcome	(Refs.)
Sakurai <i>et al</i>	Anisomycin 2 mg/ml in 99.5% ethanol BIRB796 or JNK-IN-7s solution (p38 inhibitors)	-Eight-to 12-week-old female mice C57BL/6 -IL-17A-deficient mice and keratinocyte-specific p65 and c-Rel double-knockout mice -Cell culture	-Scale -Erythema -Cytokine expression	-Topical treatment with a p38 MAPK activator induced psoriatic dermatitis <i>in vivo</i> -Topical treatment with a p38 inhibitor suppressed development of anisomycin-induced dermatitis -Topical treatment with a p38 inhibitor suppressed development of imiquimod-induced dermatitis -Attenuated modification in IL-17A deficient mice	(40)
Meng <i>et al</i>	Celastrole in miosomes gel	-Female C57/BL6 mice, aged 7-9 weeks, IMQ model 3 g cream, 5 days	-PASI -Weight ratio of spleen to body -Cytokine level evaluation	-Improved PASI (P<0.05) -Significantly different spleen/body ratio compared with the IMQ model group (P<0.05)	(43)
Ho <i>et al</i>	C16, C16SP (C16-derived short peptide; DITYVRLKF)	-BALB/c mice; IMQ model, 6 days	-Ear thickening -Epidermal thickness -Inflammatory responses in skin	-Inflammatory cytokine content (IL-22; IL-23p40; IL-17; IFN- γ) -Significantly different compared with the IMQ model group (P<0.05) -Treatment with C16 and C16SP reduced the ear thickening compared to IMQ/vehicle group (432 \pm 21 and 437 \pm 22 vs. 592 \pm 18 μ m) (P<0.0005 vs. IMQ/vehicle treatment) -C16 and C16SP led to a reduction in epidermal thickness (35.3 \pm 4.1 and 39.2 \pm 2.7 μ m, respectively). -Decreased IL-12, IL-17A, IL-6, IL-22 (P<0.0001 vs. IMQ/vehicle-treated group)	(44)

IMQ, imiquimod; PASI, Psoriasis Area Severity Index; H&E, hematoxylin and eosin; GO, graphene oxide; TPA, 12-O-tetradecanoylphorbol-13-acetate; Tregs, T regulatory cells; Sal. B, salvianolic acid B; O, oil phase; S, surfactant phase; W, water phase; DXM, dexamethasone; CAGE, choline-glyceric acid ionic liquid; BDOA, benzyl dimethyl octyl ammonium; FTIR, Fourier Transform Infrared Spectroscopy; ELISA, enzyme-linked immunosorbent assay; DC591017, ((1S)-6,7-dimethoxy-1-[2-(6-methyl-1H-indol-3-yl)ethyl]-3,4-dihydroisoquinoline-2(1H)-carbaldehyde); EPS, exopolysaccharides; CPT, calcipotriol; TQ, timoquinone; Ok, Orthokeratosis; EV, ethosomal vesicle; SBKT, sea buckthorn oil; T.A., topical application; INDO, indomethacin; TEWL, transepidermal water loss; MTX, methotrexate.

used. Using the IMQ model, Ho *et al* showed that topically administered C16 reduced epidermal hyperplasia, neutrophilic infiltrate and expression of pro-inflammatory mediators. Thus, $\alpha 5\beta 1$ integrin is a potential target for anti-psoriasis therapy (44) (Table II).

4. Discussion

After studying the scientific literature from the last current year regarding the topical therapy of psoriasis, it was observed that the subject is of great interest, with multiple experimental research studies of new therapies or mechanisms of action of already known substances included in superior formulas, with increased skin absorption and penetrability.

Imiquimod (IMQ) can aggravate and even trigger psoriasis both at the site of application and remotely. The application of imiquimod to laboratory mice causes IL-23/IL-17 axis-dependent changes, with influx of immune cells and cytokines such as IL-1 α , IFN- α , IL-23 and IL-6. On the other hand, the application of IMQ causes, possibly through a cAMP-dependent mechanism, epidermal hyperplasia, thus resulting in phenotypic and histological changes of psoriasis (45, 46). This model was initially reported in 2009 and has been used most frequently in anti-psoriasis therapy research ever since. It consists of the topical application of IMQ to the ear and back of the laboratory mouse on day 0 of the experiment demonstrating the characteristic changes of psoriasis: Erythema, scale, and altered keratinocyte differentiation. The best results have been obtained by using B6/C57BL mice (47).

The current trend regarding the therapy of psoriasis is to use vehicles such as vesicular systems (liposomes and ethosomes). Liposomes are artificial spherical vesicles composed of cholesterol and natural phospholipids. They are hydrophobic and hydrophilic, biocompatible, non-immunogenic and increase the therapeutic index and efficacy of the active substance. The properties of liposomes differ depending on composition, size (from 0.025 to 2.5 μm) and preparation methods (48).

Liposomes are used with promising results for intracellular release systems: Antisense molecules, ribosomes, proteins, and DNA (48). Ethosomes are phospholipid elastic nanovesicles with a high ethanol content (20-45%). Ethanol increases permeability and by interacting with the lipid polar end decreases the melting point of lipids in the stratum corneum, thus increasing cellular fluidity and permeability. Ethosomal systems are much more efficient in delivering the substance in terms of quantity and depth than liposomes and hydroalcoholic solutions (49). Niosomes are vesicles with non-ionic surfactant, lamellar structures formed by the combination of alkyl-polyglycerol surfactant with cholesterol. The concentration of cholesterol in liposomes is higher than that in niosomes so that the binding efficiency of the active substance is lower in the case of liposomes, which are less stable but also more expensive (50).

There were additional articles that did not meet the chosen criteria but were significant in regards to novel methods in psoriasis therapy.

Stress as an aggravating factor of psoriasis was analyzed using the imiquimod model in laboratory mice using a bottle emptying as a stressor stimulation. Thus, it was shown that stress worsened and prolonged imiquimod-induced psoriasis

dermatitis, with increased levels of neurotransmitters such as substance P and IL-1 β and IL-23p40 upregulation (51).

Estrogen receptors have been studied in relation to the development of psoriatic dermatitis in the IMQ model in laboratory mice. In one study, from day 2 of IMQ application, estrogenic agonists were administered orally: Either ER α selective agonist [propylpyrazoletriol (PPT) 2.5 mg/kg] or ER β selective agonist [diarylpropionitrile (DPN) 2.5 mg/kg]. Administration of PPT induced pruritic behavior and proinflammatory response, increasing the levels of IL-17 and IL-22, while DPN did not influence these aspects in any way. In addition, PPT also increased IL-23 levels by stimulating dendritic cells. This research concluded that the stimulation of α and not β estrogen receptors is associated with pruritic and proinflammatory behavior in the IMQ model (52).

The IMQ psoriasis induction model was used to study the mechanism of TNF- α induction by FGF-7, using a specific anti-FGF-7 antibody called F-9 which decreased inflammation and PASI. It has thus been shown that a potential therapeutic target in anti-psoriasis therapy is the FGF-7 pathway (53). Recent research by Borek *et al* (54) showed that TGF- β -dependent factors in psoriasis plaque act mainly through the bone morphogenic protein (BMP) cascade with the influence of Langerhans cell subtype, promoting the classic changes in psoriasis. *In vivo* experimental models with Junf/fJunBf/fk5cre-ERT mice were used for this purpose. Thus, it can be concluded that by using the BMP pathway as a therapeutic target, the mechanism of psoriasis production can be suppressed (54).

Microglial healing peptide-1 (MHP1-AcN) inhibits Toll-like receptor (TLR)-related inflammation by RANK/RANK-L signaling in microglia and macrophages without activating osteoclasts. Inhibition of TLR is a feasible treatment strategy for psoriasis. Using the IMQ model, the effect of this substance was studied. The results were more than promising. In addition to a reduction in erythema and scales, there were significant decreases in IL-6, IL-23, and IL-17A (55).

Kaempferol, a natural flavonoid, was found to attenuate inflammation in the imiquimod model, decreasing the proinflammatory cytokines IL-6, IL-17-A, TNF- α , inhibiting the NF- κB pathway, suppressing T lymphocytes *in vitro* and demonstrating anti-psoriasis potential (56).

5. Conclusions

Recent studies in topical psoriasis underline the importance of animal experimental research in dermatology, providing a starting point for developing new therapeutic approach in one of the most frequently diagnosed chronic diseases. Two trends can be found from the review. One trend is represented by the discovery of new topical active substances with potential anti-psoriasis effect: Lycopene, sodium butyrate, salvianolic acid B, albendazole, phosphodiesterase 4 inhibitors, thymoquinone, and nitidine chloride. Another trend is represented by the research of new mechanisms of action for some active substances, already used in the topical therapy of psoriasis but in superior topical formulations in order to increase their topical bioavailability. Vesicular systems are now providing the best vehicle for topical therapy, thus easing the action of the active substances at the target site.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

DAMN analyzed the data from the literature regarding substances and their mechanism of action. MN analyzed the results. AM designed the final aspect of the manuscript. MC analyzed the clinical implications of the new formulas researched. OAC analyzed all of the data and wrote the conclusions. All the authors critically revised the manuscript and read and approved its final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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