Systematic Review/Meta-analysis

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# Effect of topical treatment with urea in ichthyosis, atopic dermatitis, psoriasis, and other skin conditions—a systematic review

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**Introduction:** The urea composition has a profound effect on skin disorders, specifically xerosis, desquamation, and scaling, which are some of the main concerns of the current health industry. The application of urea is relatable and more bioactive than alternate treatments. The objective of this systematic review was to evaluate the effectiveness of topically applied urea in the treatment of ichthyosis, psoriasis, and other dermatologic conditions.

**Data and sources:** Research articles were retrieved through electronic databases, including Google Scholar, PubMed, EMBASE, Elsevier, and Sage, selected based on the provision of online free literature from its inception till November 2023. The significant findings were skin dryness, transepidermal water loss (TEWL), and eczema.

**Study selection:** A total of 1826 studies have been found, of which 31 were selected based on inclusion criteria. The primary reason for the exclusion of the studies was the application of urea as a control. All in vivo studies disclosed the effectiveness of urea treatment separately or in addition to another compound on skin conditions. The selected studies have reported findings related to the improvement in xerosis, erythema, scaling, and reduction in TEWL.

**Conclusion:** According to the in-depth review of the research articles, the application of urea has a tremendous effect on different skin diseases. Still, its role as monotherapy is overlooked due to the presence of more susceptible alternate products that need to be addressed. However, in the future, the evaluation of the effects of treatment containing urea with antibiotics on skin diseases would be more beneficial for practical knowledge.

**Keywords:** dermatology, disorders, skin, urea

## Introduction

The average adult's water reserves range from 60 to 65% of body weight (40 L). The 10% of that is contained in the skin, primarily in the dermis[1]. The epidermal layer of the skin contains about 120 mL of water, of which 20 mL resides in the stratum corneum. Hygroscopic substances within the corneus layer maintained the appropriate water level. These substances, also known as natural moisturizing factors, include amino acids (predominantly serin), pyrrolidone-carboxylic acid, lactic acid, sugars, and minerals[2]. The polar molecule urea ($CH_4N_2O$) is a significant part of the epidermis' natural moisturizing factor, from which it helps maintain skin wellness and hydration through its hygroscopic qualities[3,4]. It comprises a carbonyl group attached to two amine molecules and has a low molecular weight. It is produced within the body after protein metabolism in the liver. Urea has the capability of absorbing water. Its reduction causes a low hygroscopic magnitude of the epidermis with increased transepidermal water loss (TEWL), hyperkeratosis, and pruritis. It disrupts epidermal proliferation with a decreased rate of desquamation[3,5,6].

Due to its antimicrobial properties, urea was applied as a topical agent in treating wounds. Urea has been involved in dermatological conditions for the past several years in the form of cream, lotion, and foam, with different compositions and concentrations, including low and medium concentrations[7,8]. The concentration of urea regulates how it functions depending on the condition. In formulations with lower concentrations, it offers primary skin care and improvement in xerosis, while in medium concentrations, it is suggested for treating atopic dermatitis (AD), psoriasis, and ichthyosis. It is a topically applied emollient, refreshing, and antipruritic agent. At the same time, it could be performed as a keratolytic agent at high concentrations because of its effect on the amino acid arrangement, including bond lysis or morphological changes[4,9]. Topical application

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could result in mild skin irritation at high concentrations, but it is normally temporary[4].

Ichthyosis refers to a group of genetic skin disorders characterized by dry, scaly skin that resembles fish scales. It results from an abnormality in the skin's natural shedding process, leading to the accumulation of thick, rough scales. Severity varies widely, from mild to life-threatening forms. The most common type, ichthyosis vulgaris, appears in early childhood and often improves with age. Treatment focuses on moisturizing the skin and exfoliating to reduce scaling[10]. AD is a chronic, inflammatory skin condition commonly known as eczema. It causes red, itchy, and swollen skin, often appearing in childhood and persisting into adulthood. AD is associated with a dysfunctional immune response and a defective skin barrier, leading to increased susceptibility to irritants and allergens. Environmental factors and genetics play significant roles. Management includes moisturizing, avoiding triggers, and using topical corticosteroids or immunomodulators during flare-ups[11]. Psoriasis is a chronic autoimmune skin disorder that accelerates the growth cycle of skin cells, resulting in thick, silvery scales and inflamed, red patches. It commonly affects areas like the elbows, knees, scalp, and lower back. Psoriasis can vary in severity and is often associated with other conditions like psoriatic arthritis. Triggers include stress, infections, and certain medications. Treatment ranges from topical therapies to systemic medications and biologics, aimed at reducing inflammation and slowing skin cell production[12].

The most prevalent skin disorders have a common factor, i.e., dryness. However, dryness is not itself a disease. Its severe form is called xerosis, presented with smooth and wilted scaling along with the indication of skin lines, but redness, pruritus, and eczema could be conditional. Xerosis could result from lowered humidity, excessive exposure to sunlight, harsh dressing, or the continuous application of soap and other lipid solvents[13]. Atopic dermatosis is also a common skin disorder in which the preventive function of the skin is disrupted along with skin dryness[14]. The treatment regimen for the most prevalent skin disorders includes some concentration of urea; in some cases, monotherapy with urea is advised. Currently, there is no systematic review.

At present, the authors and clinicians need to be aware of systemic findings that exclusively highlight the benefits of urea treatment in skin disorders. This systematic review hypothesized that urea or urea-derived products could positively impact healing and reduce the symptoms of common skin disorders. So, the objective of the current systematic review includes supporting the present hypothesis and extensively authenticating the effectiveness of urea application in treating skin disorders.

## Methodology

This systematic review was conducted and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Assessing the Methodological Quality of Systematic Reviews guidelines, ensuring rigorous methodological standards and transparency[15]. This study was designed based on the (Introduction – Method – Results – and – Discussion) outline, as it has provided a complete and comprehensive platform for research presentation. The selection of relevant research articles, case reports, clinical trials, and comparative studies has been made under the constructed hypothesis mentioned in the population, intervention, comparison, and outcomes (PICO) principle, as shown in Table 1.

**Table 1**

**Population, intervention, comparison, and outcomes model**

| | |
|---|---|
| Participants | Studies included different skin disorders, mainly ichthyosis, atopic dermatitis, psoriasis, and other conditions |
| Interventions | Studies included urea treatment as monotherapy or combined with other substrates but should have the central focus of the study |
| Comparison | Comparators include other treatments, placebos, and no treatment |
| Outcomes | The primary outcomes of interests is the recovery of skin conditions |

## Search strategy

Different MeSH terms obtained from titles have been used in the search strategy, as seen in Table 2. Also, Boolean operators, including "AND," "OR," and "NOT," are used to speed up the search process effectively. "AND" was preferably used between "Urea," "Skin diseases," "dermatology," "Xerosis," "Urea based cream," and "Ichthyosis." To extend the search process further, "OR" has been used to differentiate between "Urea" and "Urea treatment," "Urea based cream" and "Urea derived products," "Skin diseases" and "Skin disorders," "Xerosis," and "Skin dryness." To exclude studies addressing skin treatment through interventions other than urea, including glycerine, "NOT" was operated on.

## Data extraction strategy

Google Scholar, PubMed, EMBASE, Elsevier, Sage, and Cochrane Central Register of Controlled Trials were the databases and search engines incorporated for the systematic selection of studies. Specific terminologies were used to specify related articles. The search process has been refined through filtration. Original reports from in vivo studies published from their inception till November 2023 were selected. These studies were analyzed critically to collect relevant data and information on the urea treatment of skin diseases. Studies focused on the in vivo application of urea or urea-based compounds. The search process was simplified using the PICO model, which enhances its results (Table 1).

**Table 2**

**Keywords for search strategy**

| Sr. No | Search strategy |
|---|---|
| PubMed, EMBASE, Elsevier, CENTRAL | Urea [Abstract & Keywords] OR Skin diseases [Abstracts & Keywords] OR Urea treatment [Abstract & Keywords] OR Skin disorders [Abstract & Keywords] OR Ichthyosis [Abstract & Keywords] OR dermatology [Abstract & Keywords] OR Urea-based cream [Abstract & Keywords] |
| Sage | Urea treatment [tw] OR Urea [tw] OR Skin diseases [tw] OR Skin disorders [tw] OR Ichthyosis [tw] OR dermatology [tw] OR Urea-based cream [tw] OR Xerosis [tw] |
| Google Scholar | Skin diseases [Abstract & Keywords] OR Urea treatment [Abstract & Keywords] OR Urea [Abstract & Keywords] OR Skin disorders [Abstract & Keywords] OR Ichthyosis [Abstract & Keywords] OR Urea-based cream [tw] |

## Inclusion criteria

Published studies, including cross-sectional research, randomized control trials, clinical controlled trials, pre- and post-cohort studies, and comparative research articles, were selected for this review. The included in vivo studies examined the alteration in the clinical features, TEWL, and epidermal barrier after applying urea-based treatment. Studies have used different treatment regimens, treatment durations, and evaluation criteria. These studies have been presented in the English language. They had accurate and standardized qualitative and quantitative data and analysis regarding the research topic. The studies included were the original articles, including in vivo experiments with a high impact factor.

## Exclusion criteria

Studies with improper data and their analysis, incompatibility with results, and conflicting titles have been rejected. The studies published in any language other than English were also dismissed. Some studies show restrictions while accessing their full text, which leads to their exclusion. Also, unpublished data from the thesis and dissertation were excluded during the literature search.

## Data extraction and risk of bias

Following the PICO approach, the two authors carefully examined and chose to include all research (Table 1). Titles and abstracts were screened for relevance based on predefined inclusion and exclusion criteria. Studies that passed the initial screening were subjected to a full-text review for eligibility. The investigators retrieved and classified studies by population, research category, redundant information, whole text documents, and empirical research by applying Microsoft Excel software and a predefined proforma of data extraction, making the systematic review technique achievable. The methodological characteristics were evaluated by the two authors employing the Cochrane Bias Methods Group's 7-item risk of bias assessment. The PRISMA protocol and flow chart were utilized in this review to reduce the possibility of bias. Bias was investigated in results, sample, search strategy, data insufficiency period, and site.

## Methodological quality assessment

The McMaster Questionnaire for Review of Criticism for Quantitative research papers was intended to evaluate the strategic excellence of the papers incorporated into the review[16,17]. The McMaster Review Form is composed of eight main points, including the objective of the study, literature review, research design (all interventional), population (population's detail, sample size proof, rules of conduct, and authorization), effect (authenticity and justifiability, affected domains and operations implied), treatments (details, irregularity, and co-involvement), results (significance in statistics and practical, techniques for assessment and withdrawal), and conclusion concerning the clinical situation (restriction and predisposition).

The McMaster Questionnaire for Review of Criticism for Quantitative research papers was amended to incorporate items on group allocation and the reliability of the evaluation procedures used to determine skin disease detection. All elements were assigned a positive, i.e., yes, negative, i.e., no, not addressed, or not applicable (NA) grade. A grade of "1" was given to "yes" and a score of "0" to "no and not addressed," but if the "NA" type was used, the overall grading was adjusted appropriately. The research exterior, pertinent parts, and the highest quality (17) possibly determined the overall grade. Two independent reviewers evaluated the operational excellence of the selected articles individually, and any disagreements were addressed by dialogue.

## Results

### *Electronic database search*

Extraction of articles, randomized and clinical controlled trials, and case studies was completed by searching databases such as PubMed, Google Scholar, Elsevier, Sage, and the Cochrane Central Register of Controlled Trials, which resulted in the collection of 1826 studies. The research articles have been organized based on their keywords and text terms. According to PRISMA regulations, 750 studies were removed after screening for identical and ineligible research, as shown in Fig. 1. A total of 1076 records were further screened, of which 735 were excluded due to non-relevant content. Six hundred fifty-eight papers were sought for retrieval, and 173 of them have been retrieved successfully. Finally, 33 studies were selected, and the remaining articles were not included for reasons mentioned in Fig. 1.

### *Studies were included for review and their quality assessment*

Tables 3-5 contain relevant information on selected research articles regarding skin disorders, including ichthyosis, atopic dermatosis, xerosis, and psoriasis, respectively. Conclusively, the selected research studies investigated urea's application in patients with skin treatment. The methodological evaluation of the chosen research has been mentioned in Table 6. According to the results, only six studies have mentioned details regarding dropout and the method[18-23]. A more significant concern was the justification of sample size, as the results indicate a total of 17 studies failed to provide any descriptive evidence of reason[18,20,22,24-37]. Furthermore, most articles present the outcome measures, intervention details, and the statistical representation of data. According to the risk of bias assessment, no research examined unambiguously documented sequence lineage, assignment concealment, random housing, or caregiver and investigator masking. Additionally, there were no indications of publication bias.

### *Studies focusing xerosis*

According to the observed results of the selected studies, improvement in xerosis has been seen in patients with a history of ichthyosis vulgaris. Most of the studies applied 10% cream or lotion for 3–4 weeks, and the results were analyzed clinically.

### *Studies focusing atopic dermatitis*

Studies focused on the treatment for AD applied 5–10% cream or lotion, and there was a reduction of time to relapse, improvement of dryness, itching, and erythema, and reduction of TEWL.

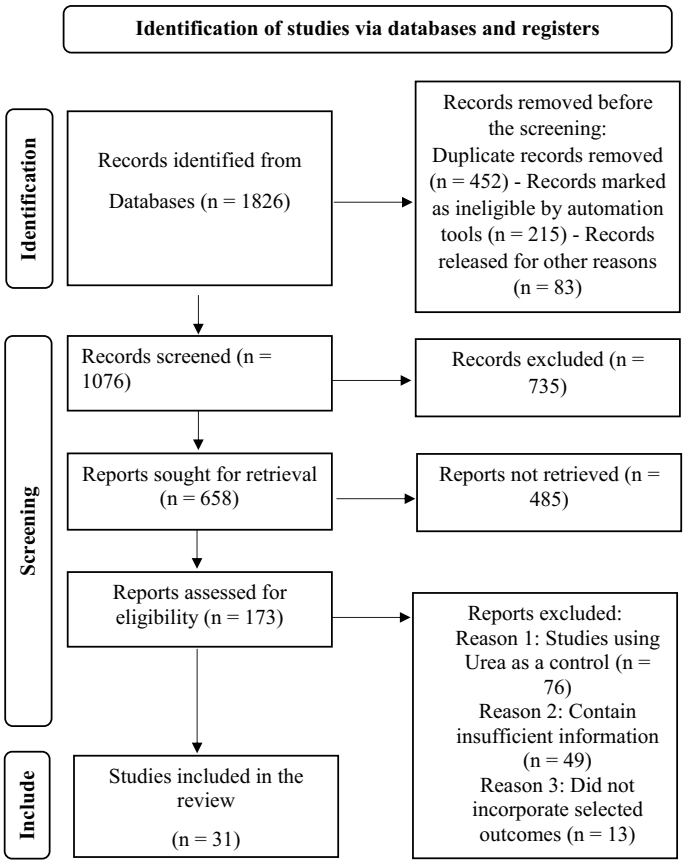


**Figure 1.** PRISMA flow diagram of the article selection process.

### *Studies focusing other skin disorders*

The rest of the studies elaborated on the effects of urea treatment of psoriasis, hand eczema, psoriasiform dermatoses of scalp, senile xerosis, sorafenib-induced hand-foot skin reactions, nickel allergic skin reactions, and palmar or plantar hyperkeratosis, with specific symptoms and observed outcomes positive in most of the studies, including improvement of scaling and erythema, improvement of xerosis and pruritus, and significant improvement in clinician's rating of skin condition.

## Discussion

The outcomes of the qualitative analysis in the selected research jointly uphold the positive impact of urea treatment in commonly prevalent skin disorders. Many studies on the application of urea have been retrieved and evaluated for their management of skin disorders. These research studies indicate that urea, alone or in conjunction with current topical therapy regimens, enhances therapeutic effectiveness while being relatively safe. However, these investigations should be analyzed with caution due to the selected articles' various time frames and durations, discrepancies in methods, and variances in analogous analysis of results.

The incorporation of urea aims to keep the epidermis hydrated by blocking the evaporation and excretion of water. Dorf *et al.* (2021), Lodén *et al.* (1999), Wire *et al.* (2009), Nasrollahi *et al.* (2018), Danby *et al.* (2022), Hagemann *et al.* (1996), Celleno *et al.* (2022), Ademola *et al.* (2002), Rosado *et al.* (2009), and Kuzmina *et al.* (2005) have all evaluated the TEWL by different methods after applying urea alone or in combination with other compounds. According to their outcomes, there was a satisfactory change in the water loss after using urea, which has the hygroscopic property to retain water predominantly[13,20,31,34,38]. However, some of these studies have exposed the treated area to sodium lauryl sulfate after applying urea, which has resulted in removing irritation after some applications. The change in TEWL and redness were reported as indicators of sodium lauryl sulfate sensitivity[18,28,30,36,39]. Also, a controlled clinical trial on 12 females with dehydrated skin on their lower legs found a statistically significant reduction in TEWL levels following twice daily use of a 15% urea cream after 2 weeks[34].

Most of the studies have reported improvement in the clinical features of the skin after urea application. The urea has been applied in different conditions of eczema, xerosis, dermatitis, psoriasis, and ichthyosis. However, in psoriasis patients, complete healing has not been observed as expected[30]. It was also observed that the moisturizer was chosen more than the lotion because the 5% urea moisturizer had an oil-in-water compound, while the 10% urea lotion had a water-in-oil composition. Although improvement in the redness, desquamation, and scaling has been significantly improved as per the pre-op symptoms in all the evaluated studies[40-44]. The Specific Symptom Sum Score is another European Expert Group on Efficacy Measurement of Cosmetics and Other Topical Products group evaluation

**Table 3.**

**Characteristics of studies conducted in patients with ichthyosis**

| Author (year) | Type of ichthyosis | Dosage and composition of urea | Comparison/ Placebo | Sample size | Intervention | Investigation | Results |
|---|---|---|---|---|---|---|---|
| Pope *et al.* (1972)[40] | Vulgaris<br>X-linked recessive | 10% Cream | 2% Salicylic acid ointment, paraffin | 37<br>47 | Daily two times for 2 weeks | Clinical | Improvement of xerosis |
| Grice *et al.* (1973)[24] | Vulgaris<br>X-linked recessive | 10% Cream | Base cream, 0.1% retinoic acid | 6<br>6 | Daily two times for 3 weeks | Water-binding capacity | Improvement |
| Fredriksson (1975)[41] | Vulgaris | 10% Cream | N/A | 30 | Daily two times for 2-4 weeks | Clinical | Improvement |
| Kuster *et al.* (1998)[42] | Vulgaris<br>X-linked recessive<br>Lamellar | 10% Lotion | 5% Lactic acid lotion | 34<br>6<br>11 | Daily two times for 8 weeks | Clinical | Improvement of xerosis |
| Tadini *et al.* (2011)[43] | Vulgaris | 10% Lotion | Glycerol-based cream | 27 | Daily two times for 4 weeks | Clinical | Improvement of xerosis |
| Benintende *et al.* (2017)[44] | Vulgaris | 10% Emulsion | None | 5 | Daily two times for 4 weeks | Clinical and instrumental (video dermoscopy and reflectance confocal microscopy) | Improvement of xerosis<br>Improvement/normalization of instrumental parameters |
| Bassotti *et al.* (2011)[45] | Lamellar | 5% Emulsion | None | 5 | Daily two times for 6 weeks | Clinical | Improvement of xerosis |
| Dorf *et al.* (2021)[18] | Vulgaris | 7.5% Cream | Glycerol-based cream | 14 | Daily two times for 4 weeks | Clinical, TEWL evaluation, and electronic skin analysis | Improvement of xerosis |

TEWL, transepidermal water loss.

technique in which an expert examines the participants' skin. This score has been implied by some of the selected studies, which also show an improved clinical condition of the condition after urea treatment[13,18,31,37]. Several trials in adults and children have established the effectiveness of products as a topical agent in treating xerosis caused by ichthyosis vulgaris[25,42-44], X-linked[42], and lamellar ichthyosis[25,45] (Table 3). Urea was examined in these studies at 5–10% concentrations, single or two times daily for 2–8 weeks, as a monotherapy or in contrast with other regimens used as a topical agent. For instance, in the most common kind of ichthyosis, ichthyosis vulgaris, urea was shown to be similarly or a little more effective in managing manifestations of skin diseases than other treatments such as glycerin[43], 2% salicylic acid + paraffin[40], and retinoic acid[24].

AD is a prevalent chronic, deteriorating, aggressive skin condition defined by muscular discomfort, dry skin, and eczema. Moisturizers, separately or in conjunction with pharmacological therapies, can ameliorate disease severity, lengthen the time between relapses, and shorten the time between episodes[46]. Several clinical trials in adults and children indicate the effectiveness of moisturizers based on urea in AD. They have also shown that they increase eczematous skin's stratum corneum moisture, water-binding capacity, and TEWL[19,26–28,38,39,47] (Table 4). A few of the selected studies have demonstrated that low doses (5–12%) may also have some advantages and can be used as a safe essential treatment for psoriasis, resulting in greater patient satisfaction[29,30] (Table 5).

Some scientific investigations back up urea's efficacy in managing xerosis compared to specified dermatological conditions (Table 5). Topical 10% urea with dexpanthenol lotion dramatically reduced skin dryness and itch in dialyzed participants in an open pilot experiment with excellent tolerability[32]. Another study found that a 10% urea ointment improved the effectiveness of lanoconazole in topical form in the management of tinea pedis manifested with hyperkeratotic skin[23]. The daily application of 10% urea and 4% lactic acid moisturizer is helpful in the direction of moderate-to-severe xerosis of the foot in diabetic individuals[33]. Prophylactic application of a 10% urea-based cream decreased sorafenib-induced hand-foot skin responses. It increased the life quality of participants in a randomized, open-label study on 871 participants with advanced hepatocellular cancer who were beginning sorafenib therapy[22]. Another trial on 53 individuals with effectively cured hand eczema found that using a 5% urea emulsion remarkably decreased the recurrence of disease symptoms[35].

The included studies varied in urea concentrations (5–10%), treatment duration, and patient outcomes. Pigatto *et al.* (1996) and Wilhelm *et al.* (1998) found improvement in dryness, itching, and erythema with 10% urea cream, while Bissonnette *et al.* (2010) showed similar benefits from both 5% and 10% urea lotions. Lodén *et al.* (1999) and Danby *et al.* (2022) demonstrated skin hydration and barrier improvements with 5% and urea-glycerol creams, respectively. This heterogeneity in concentration, duration, and population affects the generalizability of our findings across various skin conditions. Urea as monotherapy is often overlooked due to the availability of newer treatments like corticosteroids and emollients. However, urea's role in improving skin hydration and barrier function suggests potential for broader clinical use, especially in managing mild-to-moderate conditions in future guidelines. Combining urea with antibiotics could enhance treatment for skin conditions involving both barrier dysfunction and

**Table 4.**

**Characteristics of studies conducted on patients with atopic dermatitis**

| Author (year) | Dosage and composition of urea | Comparison/ Placebo | Sample size | Intervention | Investigation | Results |
|---|---|---|---|---|---|---|
| Pigatto *et al.* (1996)[19] | 10% Cream | Base cream | 70 | Daily two times for 4 weeks | Clinical | Improvement of dryness, itching, and erythema |
| Bohnsack *et al.* (1997)[26] | 10% Lotion | Vehicle cream | 41 | Daily two times for 4 weeks | Clinical; corneometry | Improvement of dryness; increase in skin hydration |
| Wilhelm *et al.* (1998)[27] | 10% Cream | Vehicle cream | 80 | Daily two times for 4 weeks | Clinical; corneometry | Improvement of itch, erythema, dryness, induration/papules; increase in skin hydration |
| Lodén *et al.* (1999)[28] | 5% Cream | N/A | 15 | Daily two times for 20 days | Corneometry; TEWL evaluation | Increase in skin hydration; reduction of TEWL |
| Wirén *et al.* (2009)[39] | 5% Cream | N/A | 22 | Daily two times for 6 months (after a 3-week treatment with betamethasone valerate 0.01% cream) | Clinical; TEWL evaluation | Reduction of time to relapse; no significant reduction in TEWL |
| Bissonnette *et al.* (2010)[47] | 5% Lotion | 10% Urea lotion | 100 | Daily two times for 42 days | Clinical | Improvement in both groups |
| Nasrollahi *et al.* (2018)[38] | 5% Emulsion | Linoleic acid emulsion | 20 | Daily two to three times for 4 weeks | Clinical; TEWL and erythema evaluation; corneometry; ultrasound | Clinical and instrumental improvement |
| Akerstrom *et al.* (2015)[46] | 5% Cream | Base cream | 172 | Daily two times for 180 days | Clinical | Reduction of time to relapse |
| Danby *et al.* (2022)[20] | Urea-glycerol cream; UGC (urea 20 mg/g and glycerol 200 mg/g are active ingredients) | Glycerol-containing moisturizer simple paraffin cream | 49 | Daily two times for 28 days | TEWL and erythema evaluation | Strengthened the skin barrier, increased NMF level, and reduced the time to replace |

NMF, natural moisturizing factor; TEWL, transepidermal water loss.

infection, such as AD and diabetic foot ulcers. Urea's hydrating properties may improve antibiotic penetration, making this combination especially beneficial for chronic wounds and compromised skin conditions. However, there are some limitations to the review. First, some of the selected studies 30 and 40 years ago could have made their methodology and intervention weak compared to the latest studies, affecting their outcomes. Second, most of the studies have follow-ups of 2 weeks, which could make the consequences doubtful regarding the safety of the urea treatment. Future studies must develop a robust research strategy, and a longer follow-up duration would be appreciated.

## Conclusion

The present investigation reveals a satisfactory number of research studies on the efficiency and protection of urea for the management of skin diseases, with different methodological qualities. While this study cannot reach conclusions, current research indicates that when added to standard therapy regimens, urea may increase treatment effectiveness. However, urea alone does not appear to be better than existing therapies.

## Ethical approval

Ethics approval was not required for this systematic review.

## Consent

Informed consent was not required for this systematic review.

## Conflicts of interest disclosure

There is no conflict of interest among the authors.


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There was no funding granted/taken for this research.


## Author contribution

Conceptualization: I.J. and M.U.A.Q. Data curation: M.U.A.Q., F.A., F.B.F., H.K., and M.J. Methodology: M.U.A.Q. and U.-e-f. Project administration: A.K. Supervision and visualization: I.J. Writing – original draft: I.J., U.-e-f., F.A., F.B.F., H.K., and V.K.K. Writing – review & editing: S.R., M.K.K., and A.R.

## Research registration unique identifying number (UIN)

Our study had already been completed before we attempted registration. As per PROSPERO guidelines, retrospective registration is not permitted for reviews that have been concluded.

**Table 5.**

**Characteristics of studies conducted on patients with psoriasis, xerosis, and other skin disorders**

| Author (year) | Disorder | Dosage and composition of urea | Comparison/ Placebo | Sample size | Intervention | Investigation | Results |
|---|---|---|---|---|---|---|---|
| Fredriksson *et al.* (1985)[29] | Psoriasis | 12% Cream | Base cream | 40 | Daily two times for 1 week | Clinical | Improvement of scaling |
| Hagemann *et al.* (1996)[30] | Psoriasis | 10% Ointment | Vehicle or no treatment | 10 | Daily three times for 2 weeks | Clinical; corneometry; TEWL; histopathology | Improvement of scaling, erythema, and induration; increase of skin hydration; reduction of epidermal thickness and proliferation |
| Celleno *et al.* (2022)[31] | Hand eczema | 30% Cream | N/A | 20 | Daily two times for 28 ± 2 days | TEWL and erythema evaluation, corneometry | Improvement in both groups |
| | Psoriasiform dermatoses of scalp | 10% Urea (foaming product) | | 20 | Daily one times for 28 ± 2 days | Desquamation index and photographic analysis of scalp | |
| Horii *et al.* (1989)[25] | Senile xerosis | 10% Cream | None | 10 | Daily four times for 2–4 weeks | Clinical | Improvement of xerosis |
| Castello *et al.* (2011)[32] | Xerosis in hemodialysis patients | 10% Lotion | None | 15 | Daily two times for 4 weeks | Clinical | Improvement of xerosis and pruritus |
| Pham *et al.* (2002)[33] | Xerosis of the feet in diabetic patients | 10% Cream and 4% lactic acid | Base cream | 40 | Daily two times for 4 weeks | Clinical | Improvement of xerosis |
| Ademola *et al.* (2002)[13] | Xerosis | 40% Cream | 12% Ammonium lactate lotion | 25 | 2 weeks | TEWL, scaliness, roughness, water content | Urea to be proven more effective than ammonium lactate |
| Grossman (2011)[21] | Xerosis | 35% Urea (foaming product) | N/A | 12 | Daily two times for 4 weeks | Clinical | Improvement of xerosis |
| Rosado *et al.* (2009)[34] | Severe xerosis | 15% Cream | N/A | 12 | Daily two times for 2 weeks | Instrumental (TEWL by tewameter) | Statistical improvement of TEWL in the treated site compared to untreated |
| Ren *et al.* (2015)[22] | Sorafenib-induced hand-foot skin reactions | 10% Cream | None | 439 | Daily three times for 12 weeks | Clinical | Usefulness in prevention |
| Lodén *et al.* (2010)[35] | Hand eczema | 5% Cream | None | 26 | Twice daily | Clinical | Usefulness in the prevention of relapses |
| Tanuma *et al.* (2001)[23] | Combination with topical lanoconazole in tinea pedis | 10% Ointment + 1% lanoconazole cream | 1% Lanoconazole cream | 23 | Daily one time for 12 weeks | Clinical | Enhanced efficacy of lanoconazole |
| Kuzmina *et al.* (2005)[36] | Nickel allergic skin reactions | 5% Cream | N/A | 25 | Daily two times for 20 days | TEWL evaluation and electrical impedance | No improvement noticed |
| Goldstein *et al.* (2008)[37] | Palmar or plantar hyperkeratosis with specific symptoms | 30% Foam | N/A | 10 | Daily two times for 28 days | Clinical (by SRRC scores) and self-assessment of QoL (by Skindx-16 Questionnaire) | Significant improvement in clinician's rating of skin condition and QoL |

SRRC, Specific Symptom Sum Score; TEWL, transepidermal water loss.

## Guarantor

Inshal Jawed.

## Provenance and peer review

No, this paper was not invited.

## Data availability statement

All of the relevant data and information have been included within the manuscript. All the data used in this analysis were collected from already published studies. Studies are available on PubMed, and data are also included in this study and, if not clear, can be requested from the corresponding author.

**Table 6.**

**Modified McMaster results of methodological quality**

| | Questions of modified McMaster critical review form | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **1** | **2** | **3a** | **3b** | **3c** | **3d** | **3e** | **4a** | **4b** | **5a** | **5b** | **5c** | **6a** | **6b** | **6c** | **6d** | **7** | **Final score (%)** |
| Goldstein *et al.* (2008)[37] | Y | Y | Y | N | N/A | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 13/15 (86.6%) |
| Kuzmina *et al.* (2005)[36] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 15/17 (82.2%) |
| Tanuma *et al.* (2001)[23] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 17/17 (100%) |
| Lodén *et al.* (2010)[35] | Y | Y | Y | N | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 14/16 (87.5%) |
| Ren *et al.* (2015)[22] | Y | Y | Y | N | Y | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 15/16 (93.7%) |
| Rosado *et al.* (2009)[34] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | N | 14/17 (82.3%) |
| Grossman (2011)[21] | Y | Y | Y | Y | N | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 15/16 (93.7%) |
| Ademola *et al.* (2002)[13] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |
| Pham *et al.* (2002)[33] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 15/17 (88.2%) |
| Castello *et al.* (2011)[32] | Y | Y | Y | N | N/A | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 13/15 (86.6%) |
| Celleno *et al.* (2022)[31] | Y | Y | Y | N | N | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 13/16 (81.2%) |
| Hagemann *et al.* (1996)[30] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 15/17 (88.2%) |
| Fredriksson *et al.* (1985)[29] | Y | Y | Y | N | Y | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 14/16 (87.5%) |
| Danby *et al.* (2022)[20] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 16/17 (94.1%) |
| Akerstrom *et al.* (2015)[46] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |
| Nasrollahi *et al.* (2018)[38] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |
| Bissonnette *et al.* (2010)[47] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |
| Wirén *et al.* (2009)[39] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |
| Lodén *et al.* (1999)[28] | Y | Y | Y | N | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 14/17 (82.3%) |
| Wilhelm *et al.* (1998)[27] | Y | Y | Y | N | Y | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 14/16 (87.5%) |
| Bohnsack *et al.* (1997)[26] | Y | Y | Y | N | Y | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 14/16 (87.5%) |
| Pigatto *et al.* (1996)[19] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 17/17 (100%) |
| Dorf *et al.* (2021)[18] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 16/17 (94.1%) |
| Bassotti *et al.* (2011)[45] | Y | Y | Y | N/A | N/A | N/A | Y | Y | Y | Y | N/A | Y | N/A | N/A | Y | N/A | N/A | 9/9 (100%) |
| Benintende *et al.* (2017)[44] | Y | Y | Y | N/A | N/A | N/A | Y | Y | Y | Y | N/A | Y | N/A | N/A | Y | N/A | N/A | 9/9 (100%) |
| Tadini *et al.* (2011)[43] | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 15/17 (88.2%) |
| Kuster *et al.* (1998)[42] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |
| Horii *et al.* (1989)[25] | Y | Y | Y | N | N/A | N/A | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 13/15 (86.6%) |
| Fredriksson (1975)[41] | Y | Y | Y | Y | N/A | N/A | Y | Y | Y | Y | Y | Y | N | N | Y | N | Y | 12/15 (80%) |
| Grice *et al.* (1973)[24] | Y | Y | Y | N | N | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 13/17 (76.4%) |
| Pope *et al.* (1972)[40] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | 16/17 (94.1%) |

McMaster items to be scored: 1 – Was the purpose stated clearly? 2 – Was relevant background literature reviewed? 3a – Was the sample described in detail? 3b – Was sample size justified? 3c – Were the groups randomized? 3d – Was randomizing appropriately done? 3e – Was the diagnostic method for onychomycosis appropriate? 4a – Were the outcome measures reliable? 4b – Were the outcome measures valid? 5a – The intervention was described in detail. 5b – Contamination was avoided? 5c – Was co-intervention avoided? 6a – Results were reported in terms of statistical significance. 6b – Were the analysis method/s appropriate? 6c – Clinical importance was reported? 6d – Dropouts were reported? 7 – Were conclusions appropriate given the study methods and results? Y = yes, N = No, NA = not applicable.

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