

RESEARCH ARTICLE

Molecular characterization of xerosis cutis: A systematic review

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Abstract

Background

Xerosis cutis or dry skin is a highly prevalent dermatological disorder especially in the elderly and in patients with underlying health conditions. In the past decades, numerous molecular markers have been investigated for their association with the occurrence or severity of skin dryness. The aim of this review was to summarize the molecular markers used in xerosis cutis research and to describe possible associations with different dry skin etiologies.

Methods

We conducted a systematic review of molecular markers of xerosis cutis caused by internal or systemic changes. References published between 1990 and September 2020 were searched using 'MEDLINE', 'EMBASE' and 'Biological abstracts' databases. Study results were summarized and analyzed descriptively. The review protocol was registered in PROSPERO database (CRD42020214173).

Results

A total of 21 study reports describing 72 molecules were identified including lipids, natural moisturizing factors (NMFs), proteins including cytokines and metabolites or metabolic products. Most frequently reported markers were ceramides, total free fatty acids, triglycerides and selected components of NMFs. Thirty-one markers were reported only once. Although, associations of these molecular markers with skin dryness were described, reports of unclear and/or no association were also frequent for nearly every marker.

Conclusion

An unexpectedly high number of various molecules to quantify xerosis cutis was found. There is substantial heterogeneity regarding molecular marker selection, tissue sampling and laboratory analyses. Empirical evidence is also heterogeneous regarding possible associations with dry skin. Total free fatty acids, total ceramide, ceramide (NP), ceramide (NS), triglyceride, total free amino acids and serine seem to be relevant, but the association

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with dry skin is inconsistent. Although the quantification of molecular markers plays an important role in characterizing biological processes, pathogenic processes or pharmacologic responses, it is currently unclear which molecules work best in xerosis cutis.

1. Introduction

Xerosis cutis or asteatosis is caused by reduced hydration of the stratum corneum and characterized by clinical signs such as small to large scales, cracks, and inflammation [1]. This is often accompanied by pruritus and risks for secondary infections [2, 3]. Besides external causes and environmental triggers [4, 5], there are endogenous or intrinsic causes of xerosis cutis such as aging, internal health conditions, dermatological and psychiatric diseases, diet and drugs [6, 7]. For example, aging related physiological changes, hormonal alteration [8], disease induced stress and inflammatory response [9] or off-target activities of drugs [10] can affect skin hydration. Although the clinical signs and symptoms are similar, it can be assumed that, as different causes are involved, there are different underlying molecular mechanisms and pathways leading to xerosis cutis. In xerosis cutis, the stratum corneum (SC) fails to maintain an adequate water concentration gradient between the living epidermal cells and the skin surface [11]. The changes may also include a decreased sebum and sweat production, inadequate cell replacement [12], disturbed skin barrier function [1] and increased transepidermal water loss [13].

The SC consists of terminally differentiated and un-nucleated keratinocytes, namely corneocytes, and a lipid matrix surrounding the cells [14]. The lipid matrix contains cholesterol, ceramides, fatty acids, cholesterol sulfate, glucosyl ceramides, phospholipids, proteins and enzymes [15–17]. Ceramides, which are essential for an optimal lipid structure, play an important role in determining water permeability and maintaining skin barrier function [15]. In addition, natural moisturizing factors (NMFs), mainly located in corneocytes [18], contribute to maintaining SC hydration [11]. Changes in the structure, arrangement or composition of any of these components may lead to decreased SC hydration and may affect the processes regulating skin integrity [43] and normal desquamation [32].

Today, biomarkers play important roles in clinical research and in dermatology. A biomarker is considered as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” [19]. From the early 1990's, there has been growing interest in molecular markers or compounds which are associated with the occurrence and/or the severity of skin dryness. Advances in analytical methods and instrumentations facilitated the laboratory analysis of molecules and the discovery of new markers [17, 20]. However, up to present time, diagnosis of xerosis cutis is largely based on clinical methods of visual assessment using scores or classifications [21, 22]. Whether the measurement of molecular markers is useful in dry skin assessment, is unclear. It may help to diagnose the underlying cause of xerosis cutis. In addition, changes of molecular markers may help to understand and/or to measure (early) treatment responses.

However, despite the wide range of markers used in xerosis cutis research [34, 37, 41, 43], there is no agreement yet about the most accurate and useful candidates. Therefore, the aim of this systematic review was to describe and summarize molecular markers of dry skin and to describe possible associations with clinical signs and/or the severity of xerosis cutis and possible underlying etiologies.

2. Methods

2.1. Eligibility criteria

We included primary studies in humans (all age groups and all languages) reporting quantitative data of molecular markers of dry skin along with performed analytical methodologies. Xerosis caused by intrinsic processes (e.g., due to aging) or underlying internal diseases (e.g. diabetes mellitus) was in our focus. The included studies had to include the participants' age, skin areas and symptoms and/or severity of dry skin. We excluded articles that described xerosis due to external causes, such as exposures to irritants, allergens, pathogens, topical treatments and inflammatory dermatological diseases such as dermatitis, psoriasis, eczema or comparable conditions. Reviews, letters, editorials, personal opinions, posters, conference abstracts as well as pre-clinical or animal studies and in vitro studies were not included in this review.

2.2. Information sources

'MEDLINE', 'EMBASE' and 'Biological Abstracts' databases were searched concurrently via OvidSP on 29 September 2020. We also conducted an updated database search on 1 January 2021 with exactly the same search criteria.

2.3. Search strategy

We searched the above-mentioned databases with combinations of key words covering xerosis cutis, humans and molecular markers. The search was conducted for articles published between 1990 and 29 September 2020. The reference lists of all interesting articles were also searched manually to identify any additional studies that fit the focus of our review. The detailed search strategy is presented in [S1 Appendix](#).

2.4. Selection process

The retrieved titles and abstracts were independently screened by two reviewers (RA and AL). Any difference in opinions between the two reviewers was resolved by consensus or by the third reviewers (JK, AV). Full text articles of all potentially eligible studies were independently checked for eligibility by the reviewers (RA and AL) and then finalized by discussion with a third author.

2.5. Data collection process

From the included studies, two reviewers extracted data regarding main outcomes of the primary studies, details about study, study participants, intervention (if any) and quantification methods. A standardized data extraction form was used. If needed, quantities of molecular markers were extracted from graphs or figures. Study results were summarized descriptively.

2.6. Data items

The following items were extracted: author's name, publication year, study design, country/ethnicity, signs of dry skin and scoring method, analyzed material, sampling technique, method of analysis, number of participants, age, sex, skin areas, severity of dry skin, molecular markers, results and quantification units ([S2 Appendix](#)).

2.7. Risk of bias assessment

There are no accepted standards or methodological guidance how to best quantify molecular markers in skin research. In Addition, the objective of this review was to describe the occurrence and characteristics of the molecular markers. Therefore, a formal risk of bias assessment was not conducted.

2.8. Effect measures

Differences between groups and the degree and strength of associations were considered as effect measures.

2.9. Synthesis methods

Extracted study results were analyzed descriptively. In order to detect possible group differences, a simplified evaluation scheme was applied: differences between proportions or quantities of molecular markers between normal and dry skin of more than 10% were considered to indicate possible associations ('Yes, higher/ lower in dry skin'). Differences between 5% to 10% were considered unclear and indicated with a question mark (?). Any difference lower than 5% was considered as biological variation ('No').

When molecular markers were presented for at least three or more different dry skin severities, a consistent increase or decrease of the marker quantity with the corresponding category was considered as a possible association. One or two deviated values in the 'trend pattern' were considered as unclear association. If there were no differences among the markers' values in relation to different dry skin severities, an association was considered unlikely. A summary of possible association was made for all the markers presented in each included article. A list of top markers was prepared considering the numbers of studies reported the corresponding markers (at least two studies). Markers analyzed once were listed separately.

3. Results

3.1. Study selection

A total of 1858 records were yielded from electronic searches in 'Medline', 'Embase' and 'Biological Abstracts' databases via OvidSP. Based on title and abstract screening, 1675 records were excluded. The remaining 183 publications were retrieved for full text evaluation along with 13 more articles which were found while searching in reference lists. Out of these 196 references, 175 publications were excluded as they did not meet the inclusion criteria. Finally, 21 articles were included for data extraction [23–43] (Fig 1).

3.2. Study characteristics

Thirteen studies were designed as cross-sectional, four as randomized control trials, two as controlled clinical trials, two as case controls and the remaining one as pre-post study. Four studies were conducted in America, nine in Asia and eight in Europe. The sample size ranged from 13 to 159 and the age of the subjects ranged from 23 to 94 years. Two studies did not report the participant's age, six did not report participant's sex and six studies did not assessed the severity of dry skin using a classification or scoring method.

Different forms of xerosis cutis were investigated. Among the included articles, five examined elderly participants whose dry skin conditions were indicated either to be associated with aging [26] or as senile xerosis [25, 28, 33, 38] where especially older people had dry skin. Here, we represented this condition as 'senile xerosis'. Skin dryness of persons with diabetes is described as diabetic xerosis which may be considered as one particular form of xerosis cutis.

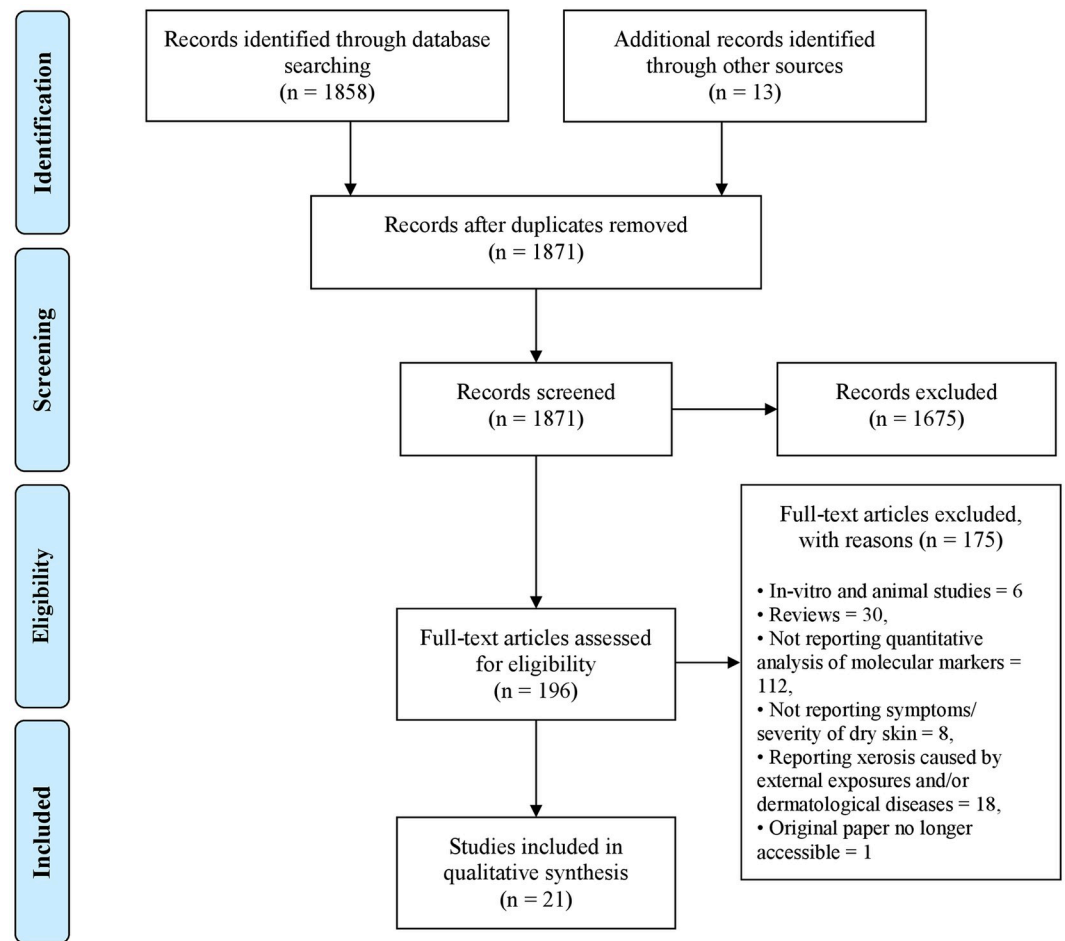


Fig 1. Flow diagram of the literature search and study selection process.

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One study, which investigated dry skin in cancer patients whose skin dryness was induced by oral intake of erlotinib drug, is reported as drug-induced xerosis [43]. Two studies analyzed markers in the dry skin of patients undergoing hemodialysis [23, 29]. In all other articles, where studies were conducted on apparently healthy participants (not mentioning any underlying internal condition), the subject's skin dryness was referred to as 'general skin dryness'.

3.3. Results of individual studies

Study details and results of the data extraction are shown in [S2 Appendix](#). A summary of results is shown in [Table 1](#). Overall, 72 markers were identified. They were sampled from eight skin areas. Most often, liquid chromatography was used as the analytical method. Molecular markers were inductively categorized into (1) lipids, (2) NMFs, (3) proteins and (4) metabolites or metabolic products.

3.3.1. Lipids. In different types of dry skin, 25 lipid and lipid like markers were reported. The markers include ceramides (14 parameters), free fatty acids (four parameters), triglyceride, cholesterol, cholesterol sulfate, total lipid, sterol esters, free sterol and wax.

3.3.1.1. Total ceramide. All the three studies which analyzed total ceramide in dry skin of patients affected by senile xerosis and diabetic xerosis [24, 28, 41], found this marker to be

Table 1. Summary of main findings (n = 21 studies).

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Hanada et al. [23]	1984	Haemodialysis patients with dry skin and sweat suppression (n = 5); and healthy volunteers (n = 8)	Not reported	Forearm	Atomic absorption spectrophotometry	Aluminium level in the epidermis Aluminium level in the dermis	Yes, higher in dry skin of haemodialysis patients
Saint-Léger et al. [24]	1988	Subjects with xerosis and subjects with normal skin (in total, n = 50)	25 to 75	Lateral mid-calf	Photodensitometry	Sterol esters in stratum corneum Triglycerides in stratum corneum Polar lipids in stratum corneum Free fatty acid in stratum corneum	Yes, lower in dry skin. Yes, lower in dry skin. Higher in dry skin. Unclear, higher in dry skin(?)
Horii et al. [25]	1989	Subjects with mild xerosis (n = 10), moderate xerosis (n = 8), severe xerosis (n = 5) and subjects with normal skin (n = 7)	59 to 94	Outer aspect of the lower legs	Amino acid analyser	Cholesterol in stratum corneum Amino acid in stratum corneum	No Unclear
Saint-Léger et al. [26]	1989	Subjects with xerosis (n = 52) and subjects with normal skin (n = 12)	30 to 40	Outer aspect of the lower legs	Photodensitometry	Wax esters and sterol esters in stratum corneum Triglycerides in stratum corneum Free Fatty Acids in stratum corneum Free sterols in stratum corneum Ceramide I in stratum corneum Ceramide II in stratum corneum Ceramide III in stratum corneum Ceramide IV and V in stratum corneum Ceramide VI in stratum corneum Cholesteryl sulfate in stratum corneum	Yes, lower in dry skin. Unclear, lower in dry skin(?) Yes, higher in dry skin. No No No No No No No No No
Jacobson et al. [27]	1990	Old subjects with dry skin (n = 13) and non-dry skin (n = 7); young subjects with dry skin (n = 8) and non-dry skin (n = 18)	60 years or older	Outer aspect of the lower legs	High performance liquid chromatography	Total stratum corneum lipids Aspartic acid in stratum corneum Threonine in stratum corneum Serine in stratum corneum Glutamic acid in stratum corneum Glycine in stratum corneum Alanine in stratum corneum Valine in stratum corneum Methionine in stratum corneum Isoleucine in stratum corneum Leucine in stratum corneum Tyrosine in stratum corneum Phenylalanine in stratum corneum Lysine in stratum corneum Histidine in stratum corneum Tryptophan in stratum corneum Arginine in stratum corneum Ornithine in stratum corneum	No Unclear, lower in dry skin(?) Unclear No Unclear, lower in dry skin(?) Unclear, higher in dry skin(?) Unclear, lower in dry skin(?) No No Unclear, higher in dry skin(?) Unclear, higher in dry skin(?) Unclear, higher in dry skin(?) No No Unclear, lower in dry skin(?) No No No No

(Continued)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Akimoto et al. [28]	1993	Older subjects with xerosis (n = 25), their age matched control (n = 20) and young control group (n = 29)	24.3 to 71	Outer aspect of the lower legs	Thin layer chromatography	Total lipid in stratum corneum Total ceramide in stratum corneum Ceramide I in stratum corneum Ceramide II in stratum corneum Ceramide III in stratum corneum Hydro- ceramide I in stratum corneum Ceramide IV and V in stratum corneum Ceramide VI in stratum corneum Cholesterol sulfate Cholesterol Ester Wax in stratum corneum Triglyceride in stratum corneum Free fatty acid in stratum corneum Cholesterol in stratum corneum Urea in stratum corneum	Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Unclear, lower in dry skin(?) Yes, lower in dry skin Yes, higher in dry skin Yes, lower in dry skin Yes, higher in dry skin Yes, higher in dry skin of haemodialysis patients.
Park et al. [29]	1995	Patients with xerotic skin undergoing maintenance haemodialysis (n = 10) and healthy volunteers (n = 18)	30 to 68	Ventral forearm	Spectrophotometry	Cholesterol in stratum corneum	Yes, lower in dry skin
Rawlings et al. [30]	1996	Subjects with dry skin (n = 24)	23 to 45	Ventral forearm	Densitometric analysis Gas chromatography	Fatty acid levels in stratum corneum Ceramide levels in stratum corneum Total Ceramide in stratum corneum Free Sterols in stratum corneum Free fatty acids in stratum corneum	Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin No Yes, lower in dry skin Unclear, higher in dry skin(?)
Schreiner et al. [31]	2000	Aged subject with dry skin (n = 4), young with dry skin (n = 5) and young with normal skin (n = 10)	25.5 (SD 2.5) to 66 (SD 3)	Lower leg	High performance thin layer chromatography and Photodensitometry	Ceramide (EOS) in stratum corneum Ceramide (NS) in stratum corneum Ceramide (NP) in stratum corneum Ceramide (EOH) in stratum corneum Ceramide (AS) in stratum corneum Ceramide (AP) in stratum corneum Ceramide (AH) in stratum corneum Desmoglein 1 in stratum corneum Plakoglobin in stratum corneum Corneodesmosin in stratum corneum Corneodesmosome density in the inner stratum corneum Corneodesmosome density in the outer stratum corneum	Unclear, higher in dry skin(?) Yes, higher in dry skin Yes, lower in dry skin Yes, lower in dry skin Unclear, higher in dry skin(?) Yes, lower in dry skin No Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin
Simon et al. [32]	2001	Xerotic skin (n = 30) and normal skin (n = 26)	22 to 49	Outer aspect of the legs	SDS-PAGE, western blotting Transmission electron microscopy		

(Continued)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Takahashi et al. [33]	2004	Aged senile xerosis (n = 12), aged normal (n = 5) and young normal group (n = 10)	18 to 81	Lower leg	High performance liquid chromatography	Total amino acid in stratum corneum Aspartic acid in stratum corneum Glutamic acid in stratum corneum Citulline in stratum corneum Serine in stratum corneum Threonine in stratum corneum Arginine in stratum corneum Glycine in stratum corneum Alanine in stratum corneum Proline in stratum corneum Valine in stratum corneum Isoleucine in stratum corneum Leucine in stratum corneum Tryptophan in stratum corneum Phenylalanine in stratum corneum Urocanic acid in stratum corneum Ornithin in stratum corneum Lysine in stratum corneum Histidine in stratum corneum Tyrosine in stratum corneum	Yes, higher in dry skin Unclear, higher in dry skin(?) Unclear, higher in dry skin(?) Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, lower in dry skin Yes, lower in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Unclear, lower in dry skin(?) Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin Unclear, lower in dry skin(?) Unclear, higher in dry skin(?)
Delattre et al. [34]	2012	Postmenopausal women and young women with dry skin (n = 10); postmenopausal women and young women with normal skin (n = 10)	30 to 60	Upper leg skin	Electrophoresis, western blot, Liquid chromatography mass spectrometry	Corneodesmosin in stratum corneum Annexin A2 in stratum corneum Phosphatidylethanolamine-binding protein 1 (PEBP1) in stratum corneum	Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin
Ishikawa et al. [35]	2013	Patients with dry skin (n = 20)	32 to 57	Outer aspect of the legs	Liquid Chromatography mass spectrometry	Ceramide (NP) in stratum corneum	Yes, lower in dry skin
Schweiger et al. [36]	2013	Volunteers with dry and itchy scalp skin (n = 30)	26 to 73	Sides of the scalp	Direct analysis in real-Time mass spectrometry Fourier-transformed middle-infrared spectroscopy	Urea in stratum corneum Lactate in stratum corneum Amide band ratio I/II in scalp site Triglyceride in scalp site Free fatty acid in scalp site Total lipid in stratum corneum IL-1ra/IL-1β in stratum corneum IL-8 in stratum corneum	Yes, lower in dry scalp skin Yes, lower in dry scalp skin Unclear, lower in dry scalp skin(?) Yes, lower in dry scalp skin Yes, higher in dry scalp skin Unclear, lower in dry scalp skin(?) Yes, higher in dry scalp skin Yes, higher in dry scalp skin

(Continued)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Son et al. [37]	2015	Dry skin and hydrated skin (total n = 22)	Men: 33.8 (5.6), Women: 31.3 (4.1)	Ventral forearm	Western blotting and densitometric analyses High performance liquid chromatography	(Pro)flaggrin in stratum corneum Bleomycin hydrolase in stratum corneum Total NMFs (as free amino acid) in stratum corneum Histidine in stratum corneum Serine in stratum corneum Arginine in stratum corneum Glycine in stratum corneum Aspartic acid in stratum corneum Glutamic acid in stratum corneum Threonine in stratum corneum Alanine in stratum corneum gamma-Aminobutyric acid in stratum corneum Proline in stratum corneum Lysine in stratum corneum Tyrosine in stratum corneum Methionine in stratum corneum Valine in stratum corneum Leucine in stratum corneum Isoleucine in stratum corneum Phenylalanine in stratum corneum Tryptophan in stratum corneum Pyrrolidone carboxylic acid in stratum corneum Urocanic acid in stratum corneum	No Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin Unclear, lower in dry skin(?) Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin Unclear, lower in dry skin(?) Unclear, lower in dry skin(?) No Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin Unclear, lower in dry skin(?) Yes, lower in dry skin Unclear, lower in dry skin(?) Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin Unclear, lower in dry skin(?) Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin
Danby et al. [38]	2016	Volunteers with dry skin (n = 21)	60 to 89	Ventral forearm	Protease assay	Caseinolytic activities in stratum corneum Chymotrypsin-like activities in stratum corneum Trypsin-like activities in stratum corneum	Yes, higher in dry skin Yes, higher in dry skin Yes, higher in dry skin
Tamura et al. [39]	2016	Subjects having heavily desquamated lips, slightly desquamated lips and subjects having no desquamation on lips (total n = 40)	22 to 52	Lips	Fluorometric l-lactate assay Not found Fourier transform infrared spectroscopy Liquid chromatography mass spectrometry	Lactate in stratum corneum Pyrrolidone carboxylic acid (PCA) in stratum corneum Carboxylic acid in stratum corneum	Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin
Vymuhore et al. [40]	2018	Subjects with mild xerosis (n = 19) and subjects with normal skin (n = 15)	57 and 58 (mean)	On outside arms or the calf	Liquid Chromatography Mass Spectrometry	Ceramide (NdS) in stratum corneum Ceramide (NS) in stratum corneum Ceramide (EOP) in stratum corneum	Yes, lower in dry skin Yes, lower in dry skin Yes, lower in dry skin

(Continued)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Lechner et al. [41]	2019	Diabetic subjects with xerosis (n = 30) and non-diabetic subjects with xerosis (n = 15)	63.5 (7.8) and 56.2 (9.3)	Foot dorsum and Plantar heel	Liquid chromatography mass spectrometry	Ceramides Natural Moisturising Factors in stratum corneum Amino Acid in stratum corneum Serine in stratum corneum Pyrrolidone carboxylic acid in stratum corneum Urocanic acid trans in stratum corneum Urocanic acid cis in stratum corneum Histamine in stratum corneum Total proteins in stratum corneum Glutathione in stratum corneum Melondialdehyde in stratum corneum	Yes, higher in dry skin of diabetics Yes, higher in dry skin of diabetics Yes, higher in dry skin of diabetics Yes, higher in dry skin of diabetics Yes, higher in dry skin of diabetics Yes, higher in dry skin of diabetics No Yes, higher in dry skin of diabetics Yes, higher in dry skin of diabetics Unclear Yes, lower in dry skin of diabetics
Legiawati et al. [42]	2020	Type 2 diabetes mellitus patients with dry Skin (total n = 159)	26 to 59	Right lower extremities	Enzyme-linked immunosorbent assays	N(6)-carboxymethyl-lysine (CML) activity in stratum corneum Interleukin-1 α (IL-1 α) activity in stratum corneum Superoxide dismutase (SOD) activity in stratum corneum	Yes, lower in dry skin of diabetics Unclear Unclear, lower in dry skin of diabetics(?)

(Continued)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Uchino et. al. [43]	2020	Patients with non-small lung cancer receiving oral Erlotinib administration having dry skin (n = 18) and healthy subjects (n = 6)	50 to 85	Ventral forearm	Ultra performance liquid chromatography combined with time-of-flight mass spectrometry	Cholesterol Sulfate in stratum corneum Total free fatty acids in stratum corneum Saturated free fatty acids in stratum corneum Hydroxy free fatty acids in stratum corneum Unsaturated free fatty acids in stratum corneum Total Ceramide in stratum corneum Ceramide (NdS) in stratum corneum Ceramide (NS) in stratum corneum Ceramide (NP) in stratum corneum Ceramide (NH) in stratum corneum Ceramide (AdS) in stratum corneum Ceramide (AS) in stratum corneum Ceramide (AP) in stratum corneum Ceramide (AH) in stratum corneum Ceramide (EOdS) in stratum corneum Ceramide (EOS) in stratum corneum Ceramide (EOP) in stratum corneum Ceramide (EOH) in stratum corneum	Yes, higher in dry skin of patients receiving oral Erlotinib Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) No Unclear Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) No Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Yes, lower in dry skin of patients receiving oral Erlotinib Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?) Unclear, lower in dry skin of patients receiving oral Erlotinib(?)

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higher in those subjects. However, in drug-induced xerosis, association of total ceramide with skin dryness was unclear [43]. In general skin dryness, one study found lower level of total ceramide in the dry skin [30]. Another cross sectional study, conducted in smaller sample size (n = 5 and 10), found no association [31].

3.3.1.2. *Ceramide (NP)*. Ceramide (NP), previously known as ceramide III, was found to be lower in three studies regarding general skin dryness [31, 35, 39]. In contrast, one study in older subjects found ceramide (NP) to be remained in higher amount in senile xerosis [28]. Saint léger et. al., 1989 did not found any association of this marker with general skin dryness [26]. In drug-induced xerosis, the association was unclear [43].

3.3.1.3. *Ceramide (NS)*. In subjects with senile xerosis, the amount of ceramide (NS), previously ceramide II, was found in lower amounts than their age matched control [28]. Two studies on general skin dryness also found this marker to be associated with dry skin but they reported opposite results to each other [31, 40]. Another study with similar setting did not find any association [26], while in the case of drug-induced xerosis, an association was unclear [43].

3.3.1.4. *Ceramide (EOS), ceramide (NH) and ceramide (EOH)*. These three members of ceramide subclasses were found to be positively associated with senile xerosis [28] but negatively associated with general skin dryness [31, 39, 40]. However, one study showed no association of these ceramides with general skin dryness [26] and another study showed it to be unclear [43].

3.3.1.5. *Ceramide (AS) and hydroceramide I*. Ceramide (AS) and hydroceramide I were only found to be associated with senile xerosis and the reported amount was higher in the aged dry skin [28]. However, additional studies which analyzed ceramide (AS) in other dry skin conditions (general skin dryness and drug-induced xerosis), reported either unclear or no association [26, 31, 43].

3.3.1.6. *Ceramide (AP) and ceramide (NdS)*. All the studies that analyzed the quantitative amounts of these two ceramides, reported these markers to be present in lower amounts in different dry skin conditions. Ceramide (AP) was investigated both in general skin dryness and drug-induced xerosis [31, 43] while ceramide (NdS) was only analyzed in general skin dryness [40].

3.3.1.7. *Ceramide (AH), ceramide (AdS), ceramide (EOdS) and ceramide (EOP)*. No study reported any positive or negative association of these four ceramides with any type of xerosis cutis.

3.3.1.8. *Total free fatty acids*. Seven studies published between 1988 and 2020 analyzed total free fatty acids, of which four reported associations of this marker with different dry skin conditions [26, 28, 30, 36]. Akimoto et. al., 1993 found the amount of free fatty acid to be lower in older subjects with xerosis than their age matched control [28]. Two studies on general skin dryness (one cross sectional, another, randomized controlled trial) found opposite results to each other; higher [26] and lower [30]. The amount of free fatty acids were found higher in dry and itchy scalp skin compared to the side of the scalp which achieved reduced dryness after a tonic treatment [36]. Results reported by other three studies were found to be unclear [24, 31, 43]. Uchino et. al., 2020 [43] also analyzed three categories of free fatty acids in the dry skin of patients receiving erlotinib drug. Unsaturated free fatty acids were not associated with drug-induced xerosis while saturated and hydroxyl free fatty acids revealed unclear association.

3.3.1.9. *Triglycerides*. Two studies on senile xerosis reported the association of triglycerides with skin dryness. One study found this to be higher in aged dry skin compared to the control sample while another study found the opposite [24]. In general skin dryness, one study found no association [26] but in dry scalp skin, the amount of triglycerides was comparatively lower when the scalp was found to be drier [36].

3.3.1.10. *Cholesterol and cholesterol sulfate*. Studies, where an association was present, both of these two markers were shown to be in lower amounts in general skin dryness [30] and in higher amounts in senile xerosis and drug-induced xerosis [28, 43]. However, there is also one

study per marker, which reported no association of cholesterol and the sulfate ester of this compound with dry skin.

3.3.1.11. Free sterols, sterol esters and wax. Like cholesterol, total free sterols and total sterol esters were also found to be in lower amounts in general skin dryness [26, 31], but unlike the sulfate ester, total sterol esters [24] and wax [28] were found to be in lower amounts in senile xerosis [24, 28]. There are also other studies in this review, which reported unclear association of sterol esters in senile xerosis [28] and no association of free sterols in senile xerosis [26].

3.3.1.12. Total lipids. Three studies reported this marker, one study described an association [28], one described an unclear association [36] and the remaining study described no association [26] with skin dryness. In the study where an association was found, a higher amount of total lipid in senile xerosis was reported [28].

3.3.2. Natural moisturizing factors (NMFs). Twenty-five NMFs components were reported in different dry skin etiologies, which include most standard amino acids, ornithin, citrulline, gamma-aminobutyric acid, urocanic acid, carboxylic acids and pyrrolidone carboxylic acid.

3.3.2.1. Total free amino acids (FAAs) and NMFs. Total FAA was found to be higher in the dry skin of patients with underlying conditions like senile xerosis [33] and diabetic xerosis [41]. Analysis of NMFs also revealed the same pattern [41]. Inversely, in general skin dryness, the amount of FFAs was found to be lower than the control samples [37]. One study, however, found unclear association of FAAs in senile xerosis [25].

3.3.2.2. Serine, alanine, leucine, phenylalanine and threonine. These five amino acids followed the similar pattern as total FAAs. Amounts of these amino acids were higher in senile xerosis and diabetic xerosis [33, 41] and were lower in general skin dryness [37]. However there is at least one study which found either 'unclear' or 'no' association of these amino acids with general skin dryness [27].

3.3.2.3. Glycine and arginine. In both senile xerosis and general skin dryness, glycine and arginine was negatively associated [33, 37], hence, amounts were found to be lower than in the control group. Unclear or no association of these two amino acids were also reported [27].

3.3.2.4. Histidine, tyrosine, glutamic acid, tryptophan and methionine. For these five amino acids, association was reported only in case of general skin dryness and the amounts were lower compared to the control group [37]. One study on senile xerosis [33] and another study on general skin dryness [27], both worked on small control groups (n = 5 and 7), reported either 'unclear' or 'no' association of these amino acids with xerosis cutis.

3.3.2.5. Isoleucine, valine, lysine, proline, ornithin and citrulline. All these six amino acids were reported to be associated with only senile xerosis [33]. The association was positive; that means in aged skin, these amino acids were found to be in higher amounts than the control samples. Except citrulline, other five amino acids were showed to have either 'unclear' or 'no' association with general skin dryness [27, 37].

3.3.2.6. Aspartic acid and gamma-aminobutyric acid. Only unclear associations were found in general skin dryness [27, 37] and senile xerosis [33].

3.3.2.7. Urocanic acid, carboxylic acids and pyrrolidone carboxylic acid (PCA). Urocanic acid was reported to be present in higher amounts in senile xerosis [33] and also in diabetic xerosis [41]; as trans urocanic acid. However, in case of cis urocanic acid, no association was found with diabetic xerosis [41]. In general skin dryness, the association was not clear [37]. Carboxylic acids (total) followed different pattern- 'negative association' with senile xerosis [38]. When only pyrrolidone carboxylic acid was investigated, it was reported to be present in lower amounts in general skin dryness and senile xerosis [37, 38] but in higher amounts in diabetic xerosis [41].

3.3.3. Proteins/ enzymes. Described below are the 17 protein, enzyme, cytokines and similar markers which were reported in the included articles in this review.

3.3.3.1. Corneodesmosin, desmoglein 1, plakoglobin, annexin A2 and phosphatidylethanolamine-binding protein 1. These five protein markers were found to be positively associated with general skin dryness. Corneodesmosin was investigated in two studies [32, 34] while the others were studied once [32] or [34]. In all cases, the amount of these proteins were quantified in higher amounts in dry skin compared to the subjects' age-matched control. It is to be noted that in the study by Delattre et. al. 2012, who analyzed corneodesmosin, annexin A2 and phosphatidylethanolamine-binding protein 1, about half of the study population was postmenopausal women [34].

3.3.3.2. Caseinolytic activities, chymotrypsin-like activities, trypsin-like activities and total proteins. These four protein markers were found to be in elevated amounts in dry skin of patients with underlying conditions. Caseinolytic activities, chymotrypsin-like activities and trypsin-like activities were measured in senile xerosis [38]. These markers were positively associated with skin dryness. Total protein was shown to be increased in diabetic xerosis [41].

3.3.3.2. N(6)-carboxymethyl-lysine activity and bleomycin hydrolase. Being negatively associated with dry skin, N(6)-carboxymethyl-lysine activity was reported in diabetic xerosis [42] and bleomycin hydrolase was reported in general skin dryness [37]. In both cases, amount of these markers were found to be in lower amount in dry skin compared to the control groups.

3.3.3.3. Glutathione, (pro)filaggrin and superoxide dismutase activity. Glutathione, a tri-peptide, was detected in non-diabetics with dry skin though it was not found in diabetics with dry skin [41]. The association seems unclear. (Pro)filaggrin was also reported to have no association in general skin dryness [37]. The association of superoxide dismutase was unclear with diabetic xerosis as reported by Legiawati et. al., 2020 [42].

3.3.3.4. Cytokines (Interleukin (IL)-8, IL-1ra/IL-1 β and Interleukin-1 α). In scalp skin (general skin dryness), the amount of interleukin-8 was found to be higher in the dry scalp compared to the amount of this marker found in the hydrated scalp after tonic treatment. The ratio of IL-1ra/IL-1 β was also positively associated with scalp dryness [36]. Another study which measured interleukin-1 α activity in diabetic xerosis, found its association with the skin dryness to be unclear [42].

3.3.4. Metabolites or metabolic products. Five metabolites/ metabolic products including lactate, urea, histamine, melondialdehyde and aluminium were reported to be associated with dry skin.

3.3.4.1. Lactate. Both of the two studies which investigated on the amount of lactate in the skin, found this marker to be negatively associated with skin dryness. One study was on dry scalp skin (general skin dryness) [36] and another was on senile xerosis [38].

3.3.4.2. Urea. In the dry skin of patients undergoing hemodialysis, the amount of urea was found to be higher compared to control subjects [29]. The opposite was found in case of dry scalp skin (general skin dryness) where the amount of urea was negatively associated with dryness of scalp [36].

3.3.4.3. Histamine and melondialdehyde. Both of these markers were shown to be associated with the dry skin of diabetic patients compared to skin dryness in non-diabetics. Histamine, a neurotransmitter, was positively associated with diabetic xerosis while melondialdehyde, a marker of oxidative stress, was decreased in diabetic xerosis [41].

3.3.4.4. Aluminium. In the dry skin of hemodialysis patients, aluminium levels in the epidermis and dermis were higher than in the control group and seemed to be positively associated with the skin dryness [23].

3.4. Number of markers and possible associations with dry skin

[Table 2](#) presents a summary of all molecular markers, which were reported at least in two studies (top markers). Additionally, [S3 Appendix](#) is for the markers which was analyzed only in one study. Total free fatty acids, total ceramide, ceramide (NP), ceramide (NS), ceramide (NH), ceramide (EOS), ceramide (EOH), ceramide (AS), triglyceride, total free amino acids, serine and urocanic acid were measured in at least four studies. From those, the number of studies suggesting associations between molecular markers and dry skin compared to the number of studies of unclear or no associations was higher for total free fatty acids, total ceramide, ceramide (NP), ceramide (NS), triglyceride, total free amino acids and serine.

4. Discussion

This systematic review identified more than 70 molecular markers that were measured in dry skin research. In addition, various sampling and analytical methods were used. Overall, only 12 molecular markers were reported in at least four studies. The majority of markers was reported only once or twice. This indicates substantial heterogeneity in this field and makes the intended comparisons nearly impossible.

When considering the markers, which were reported at least four times, seven seemed to be associated with skin dryness in at least two or more studies (total ceramide, ceramide (NP), ceramide (EOS), ceramide (NH), ceramide (EOH), free amino acids and serine). If associated, they were always found to be lower in general skin dryness but higher in xerosis induced by any internal condition. Additional markers, which seem to show a similar pattern are cholesterol, cholesterol sulfate, alanine, leucine, phenylalanine, threonine and urea. Though these were analyzed in less number of studies, associations with xerosis cutis were reported in at least two studies. In addition, the independent association of ceramide (NP), ceramide (NH) and cholesterol sulfate was demonstrated by statistical analysis in corresponding studies [35, 39, 43].

Total free fatty acids, ceramide (NS) and triglycerides were also analyzed in four or more studies but the associations of these markers with xerosis cutis seemed unclear. For example, in general skin dryness, total free fatty acids were shown to have both positive [26, 36] and negative associations [30]. Same was also seen for ceramide (NS) [31, 40]. Triglycerides in senile xerosis also showed conflicting results [24, 28]. Moreover, for nearly every marker there were also studies showing unclear or no association. In addition to the wide variety of reported markers, this may indicate substantial biological variability. Variations may be caused by the analytical methods (e.g., SC or compounds dissolved from SC) used. In addition, use of different sampling methods (tape-stripping, varnish stripping, solvent extraction, etc) might contribute to the variability in results. Sensitivity differences among individual methods of analysis may produce remarkable variability as only six recent studies used unambiguous quantitation technology like mass spectrometry while others used different spectrophotometric techniques such as photodensitometry, thin layer chromatography, liquid chromatography, gas chromatography or other biomolecular tools depending on the analyte characteristics. Moreover, variations in study design, number of samples and reported quantitative units might also have contributed to observed heterogeneity and variability to some extent.

We also found four markers (pyrrolidone carboxylic acid, corneodesmosin, lactate and urea) which were associated with dry skin in all the few studies they were reported. PCA was analyzed in three studies with both negative [37, 38] and positive [41] association. Corneodesmosin was found to be positively associated [32, 34] while lactate [36, 38] and urea [29, 36]

Table 2. Top markers (compounds analysed more than once).

Molecular markers	Number of studies	Analysed material	Sampling technique	Method of analysis	Association with skin dryness (number of studies)
Total free fatty acids [24, 26, 28, 30, 31, 36, 43]	7	Compounds dissolved from stratum corneum/ stratum corneum/ direct measurement of skin area	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping/ shave biopsy/ direct measurement	Photodensitometry/ thin layer chromatography/ fourier-transformed middle-infrared spectroscopy/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 4 Unclear: 3
Total ceramide [24, 28–31, 41, 43]	6	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping/ shave biopsy/ collecting swabs.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 4 No: 1 Unclear: 1
Ceramide (NP); also called Ceramide III. [19, 26, 28, 31, 35, 39, 43]	6	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ varnish stripping/ tape stripping	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 4 No: 1 Unclear: 1
Ceramide (NS); also called Ceramide II. [19, 26, 28, 31, 40, 43]	5	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ collecting swabs/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 3 No: 1 Unclear: 1
Ceramide (EOS); also called Ceramide I. [19, 26, 28, 31, 40, 43]	5	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ collecting swabs/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 2 No: 1 Unclear: 2
Triglyceride [24, 26, 28, 36]	4	Compounds dissolved from stratum corneum/ stratum corneum/ direct measurement of skin area	Hexane- methanol extraction/ stripping with cyanoacrylate resin / direct measurement	Photodensitometry/ thin layer chromatography/ fourier-transformed middle-infrared spectroscopy	Yes: 3 Unclear: 1
Serine [27, 33, 37, 41]	4	Scraped cells from stratum corneum/ stratum corneum/ compounds dissolved from stratum corneum.	Scraping off the skin with a glass slide/ tape stripping/ collecting swabs	High performance liquid chromatography/ liquid chromatography mass spectrometry	Yes: 3 No: 1
Total free amino acids [25, 33, 37, 41]	4	Stratum corneum/ compounds dissolved from stratum corneum	Tape stripping/ scraping off the skin with a glass slide/ collecting swabs	Amino acid analyzer/ high performance liquid chromatography/ liquid chromatography mass spectrometry	Yes: 3 Unclear: 1
Ceramide (NH); also called Ceramide VI [19, 26, 28, 39, 43]	4	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin/ tape stripping	Photodensitometry/ thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 2 No: 1 Unclear: 1
Urocanic acid (UCA) [27, 33, 37, 41]	4	Stratum corneum/ compounds dissolved from stratum corneum	Scraping off the skin with a glass slide/ tape stripping/ collecting swabs	High performance liquid chromatography/ liquid chromatography mass spectrometry	Yes: 2 (1 as UCA trans) No: 1 (as UCA cis) Unclear: 1
Ceramide (EOH); also called Ceramide IV. [26, 28, 31, 43]	4	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 1 No: 1 Unclear: 2
Ceramide (AS) [26, 28, 31, 43]	4	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	No: 1 Unclear: 3
Pyrrolidone carboxylic acid [37, 38, 41]	3	Stratum corneum/ compounds dissolved from stratum corneum	Tape stripping/ collecting swabs	High performance liquid chromatography / liquid chromatography mass spectrometry	Yes: 3

(Continued)

Table 2. (Continued)

Molecular markers	Number of studies	Analysed material	Sampling technique	Method of analysis	Association with skin dryness (number of studies)
Glycine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Alanine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Leucine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Phenylalanine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 No: 1
Arginine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 No: 1
Threonine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Cholesterol [24, 28, 30]	3	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping	Photodensitometry/ thin layer chromatography	Yes: 2 No: 1
Cholesterol sulfate [26, 28, 43]	3	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping	Photodensitometry/ thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 2 No: 1
Corneodesmosin [32, 34]	2	Stratum corneum	Varnish stripping	Electrophoresis, western blot and liquid chromatography mass spectrometry.	Yes: 2
Lactate [36, 38]	2	Compounds dissolved from stratum corneum	Skin surface material collected by DIP-it sampler/ collecting swabs	Real-time mass spectrometry/ fluorometric L -lactate assay.	Yes: 2
Urea [29, 36]	2	Stratum corneum/ compounds dissolved from stratum corneum	Cyanoacrylate adhesive stripping/ skin surface material collected by DIP-it sampler	Spectrophotometry/ real-time mass spectrometry	Yes: 2
Ceramide (AP) [31, 43]	2	Stratum corneum	Shave biopsy/ tape stripping.	High performance thin layer chromatography and photodensitometry/ liquid chromatography mass spectrometry	Yes: 2
Histidine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Tyrosine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Glutamic acid [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Isoleucine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Tryptophan [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 No: 1 Unclear: 1
Valine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 No: 1 Unclear: 1
Total lipid [26, 28, 36]	3	Compounds dissolved from stratum corneum/ stratum corneum/ direct measurement of skin area	Hexane- methanol extraction/ stripping with cyanoacrylate resin / direct measurement	Photodensitometry/ thin layer chromatography/ fourier-transformed middle-infrared spectroscopy	Yes: 1 No: 1 Unclear: 1

(Continued)

Table 2. (Continued)

Molecular markers	Number of studies	Analysed material	Sampling technique	Method of analysis	Association with skin dryness (number of studies)
Lysine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Sterol esters [24, 26, 28]	3	Compounds dissolved from stratum corneum/ stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin	Photodensitometry/ thin layer chromatography	Yes: 1 Unclear: 2
Proline [33, 37]	2	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 1
Ceramide (NdS) [40, 43]	2	Compounds dissolved from stratum corneum/stratum corneum	Collecting swabs/ tape stripping.	Liquid chromatography mass spectrometry	Yes: 1 Unclear: 1
Methionine [27, 37]	2	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 No: 1
Ornithin [27, 33]	2	Stratum corneum	Scraping off the skin with a glass slide	High performance liquid chromatography	Yes: 1 No: 1
Free sterols [26, 31]	2	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ shave biopsy	Photodensitometry/high performance thin layer chromatography	Yes: 1 No: 1
Aspartic acid [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Unclear: 3
Ceramide (AH) [31, 43]	2	Stratum corneum	Shave biopsy/ tape stripping.	High performance thin layer chromatography and photodensitometry/ liquid chromatography mass spectrometry	No: 1 Unclear: 1

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were found to be negatively associated with skin dryness. More studies are required to evaluate the significance of these markers.

Quantitative expressions of several markers were found to be consistently changing with multiple clinical score values of skin dryness in corresponding samples. Triglycerides, ceramide (NH), ceramide (NP), ceramide (AP), urea and lactate showed gradual increase; while total free fatty acids and cholesterol sulfate were found to be gradually decreased with the reported severities of dry skin assessed according to the scoring methods. However, except urea and lactate (though reported in only two studies), other studies reported unclear or no associations of these markers which indicates heterogeneity in overall expression.

In case of dry skin induced by internal diseases, markers of diabetic xerosis was studied exhaustively in two recent studies by Lechner et. al., 2019 [41] and Legiawati et. al., 2020 [42]. Among the markers, pyrrolidone carboxylic acid was higher in diabetic xerosis; but in other dry skin conditions (general skin dryness and senile xerosis), there were negative associations. Trans-urocanic acid was positively associated but cis-urocanic acid was not associated with diabetic xerosis. Total ceramide, NMFs and histamine were positively associated while N(6)-carboxymethyl-lysine and melondialdehyde was negatively associated.

It is also well known, that the occurrence and severity of xerosis cutis is skin area specific, for example in senile xerosis the legs are drier than the arms [2]. However, the heterogeneity of the reviewed evidences makes these intended comparisons almost impossible. In addition, we did not include any study that compared skin dryness or markers from both the arms and leg skin areas.

Further research in this field is necessary to facilitate the discovery of evidence of associations of the molecular markers with skin dryness and to help in guiding clinical practice. The status of certain markers may even help clinicians in more precise understanding of the underlying causes of the disease. However, for translating the research findings into clinical practice, as recommended by Hammond and Taube [44], the markers should be validated in prospective, well-controlled clinical trials of various patient participants across different institutions with established standard for sample preparations, data collection, statistical analysis and scoring. Many studies analyzed multiple markers simultaneously. Besides considering the individual markers, a panel of markers might also provide a better inside in disease prognosis especially in xerosis cutis with underlying conditions, which merits further investigation.

One of the limitations of this systematic review is that we selected the top markers primarily based on the number of articles in which they were analyzed. We searched for particular patterns regarding the occurrence of the markers with the presence or severity of skin dryness. That is why the markers, which were analyzed only in one study, could not be placed as top markers though some might have potential as important markers. The objective of this review was to describe possible associations of molecular markers based on their quantitative patterns related to skin dryness. To define the association, an arbitrary evaluation of the patterns was used which is another limitation of this study. In addition, as the p-values are affected by the sample size, we considered the difference between the quantitative amounts of the markers found in the comparing groups rather than the reported p-values which were actually present only in few articles and unlikely to be clinically relevant. Additional limitation of this study is that, group comparisons between the skin of healthy people and the skin of people with underlying conditions might be biased as they also differ in other characteristics beyond skin dryness (diabetes, hemodialysis, hormonal imbalance, drug effects, etc.). Also, we did not include temporary skin dryness due to seasonal changes which is more logical to be described as rough skin as stated by De Paepe et.al., 2009 [45]. As we were interested in reviewing the markers studied in pathological xerosis, seasonal dry skin was not in our focus.

5. Conclusion

Seventy-two molecular markers for measuring xerosis cutis were identified. Total free fatty acids, ceramides, triglycerides, total free amino acids, serine and urocanic acid have been reported most often, but the evidence whether the quantity of these molecular markers indicates the status of skin dryness is heterogeneous. Thirty-one molecular markers were reported only once. Although there is a huge interest in molecular markers in dry skin research, it is currently unclear which are the most relevant.

Supporting information

S1 Appendix. Search strategy.

(PDF)

S2 Appendix. Study details and results of the data extraction.

(DOCX)

S3 Appendix. Molecular markers analyzed only once.

(DOCX)

S4 Appendix. PRISMA checklist. A review protocol has been registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020214173).

(DOCX)

S1 File.
(PDF)

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