eISSN 2255-0569

ORIGINAL

Inositol in Dermatologic Diseases

El Inositol en enfermedades dermatológicas

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Received: 14 - IX - 2022
Accepted: 13 - X - 2022

doi: 10.3306/AJHS.2023.38.01.29

Abstract

Background: Inositol is a natural ingredient widely used to treat metabolic conditions, hormonal regulation, and neurodegenerative diseases. However, there is a lack of discussion about the importance of inositol in the treatment of dermatological disorders.
Objectives: To systematically review the literature on the efficacy and safety of systemic inositol use for dermatologic diseases.
Methods: PubMed, Ovid/MEDLINE, and Embase in the Cochrane Library databases were searched. We included clinical trials studies and case reports of systemic inositol use among patients diagnosed with skin disorders of all ages (16 studies and 2 case reports).
Results: Inositol and its derivatives including myo-inositol (MI), d-chiro-Inositol (DCI), glycero-phospho-Inositol (GPI), and inositol hexaphosphate (IP6) demonstrated potential use for the treatment of acne, hirsutism, atopic dermatitis, seborrheic dermatitis, hidradenitis suppurativa, psoriasis, Raynaud's disease, ischemic ulcer, calciphylaxis, and melanoma. Mild gastrointestinal side effects were reported in 21 patients, which all resolved without modifying the original regimens.
Limitations: Small sample sizes, variations in treatment protocols and lack of standardized outcome measurements.
Conclusions: Inositol is a promising treatment for various dermatological disorders. Dermatologists should consider inositol as a combined therapy in their medication arsenal given its promising results, good tolerability, and relatively few side effects.

Keywords: Inositol, myo-inositol, D-chiro-inositol, metabolic diseases, dermatology.

Resumen

Antecedentes: El inositol es un ingrediente natural ampliamente utilizado para tratar afecciones metabólicas, la regulación hormonal y las enfermedades neurodegenerativas. Sin embargo, no se discute la importancia del inositol en el tratamiento de los trastornos dermatológicos.
Objetivos: Revisar sistemáticamente la literatura sobre la eficacia y seguridad del uso del inositol sistémico para las enfermedades dermatológicas.
Métodos: Se realizaron búsquedas en las bases de datos PubMed, Ovid/MEDLINE y Embase de la Biblioteca Cochrane. Se incluyeron estudios de ensayos clínicos y reportes de casos sobre el uso de inositol sistémico entre pacientes diagnosticados con trastornos de la piel de todas las edades (16 estudios y 2 reportes de casos).
Resultados: El inositol y sus derivados, incluidos el mio-inositol (MI), el d-chiro-inositol (DCI), el glicero-fosfato-inositol (GPI) y el hexafosfato de inositol (IP6), demostraron un uso potencial para el tratamiento del acné, el hirsutismo, la dermatitis atópica, la dermatitis seborreica, la hidradenitis supurativa, la psoriasis, la enfermedad de Raynaud, la úlcera isquémica, la calcifilaxis y el melanoma. Se notificaron efectos secundarios gastrointestinales leves en 21 pacientes, que se resolvieron sin modificar los regímenes originales.
Limitaciones: Tamaños de muestra pequeños, variaciones en los protocolos de tratamiento y falta de mediciones estandarizadas de los resultados.
Conclusiones: El inositol es un tratamiento prometedor para diversos trastornos dermatológicos. Los dermatólogos deberían considerar el inositol como terapia combinada en su arsenal de medicamentos, dados sus prometedores resultados, su buena tolerabilidad y sus relativamente escasos efectos secundarios.

Palabras clave: inositol, mio-inositol, D-chiro-inositol, enfermedades metabólicas, dermatología.

Capsule summary

- Inositol is a natural ingredient widely used to treat metabolic conditions, hormonal regulation, and neurodegenerative diseases, but their safety and efficacy have not been systemically reviewed in dermatological disorders.
- Most data supported Inositol as an effective alternative for treating a wide range of dermatological diseases, with relatively few side effects.

Abbreviations

AE: Adverse effect; ATP: adenosine triphosphate; BID: twice a day; BMI: Body mass index; BWAT: Bates-Jensen Wound Assessment Tool; CGI-I: clinical global impressions-improvement scale; DCI: D-chiro-Inositol; DHEAS: Dehydroepiandrosterone; FTU: fingertip unit; GAGS: global acne grading system; GID: gastrointestinal disturbance; GPI: Glycero-phospho-Inositol; HM: Myo-inositol hexaphosphate; HTN: hypertension; HS: Hidradenitis suppurativa; IGA: investigator global assessment; IGF-1: Insulin growth factor-1; IP6: Inositol hexaphosphate; IV: Intravenous; MeSH®: Medical Subject Headings; Hexopal®: Inositol nicotinate; HD: hemodialysis; mCS: modified Cook's scale; mFGHS: Ferriman-Gallwey hirsutism score; MI: Myo-inositol; NOS: Newcastle-Ottawa Scale; OCD: Obsessive-compulsive disorder; OR: Odds ratio; PASI: psoriasis area and severity index; PI: Phosphoinositides; PIP2: Phosphatidylinositol 4,5-bisphosphate; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PCOS: Polycystic ovarian syndrome; PSI: plaque severity index; QoL: quality of life; ROS: Reactive oxygen species; RP: Raynaud phenomenon; (R)TG: (reactive) therogradient; SD: Seborrheic dermatitis; SE: side effect; SRI: Serotonin-reuptake inhibitor; TH: trehalose; TID: thrice a day; TIW: thrice a week; VAS: visual analogue scale.

Introduction

The beneficial effect of dietary supplementation in clinical medicine has gained great attention in recent years and led to the development of the "functional medicine" field. In particular, physicians and scientists started to investigate vitamin/mineral/natural product supplements as an alternative to standard medication. One example is the family of inositols, which is a carbocyclic sugar consisting of nine stereoisomers of naturally occurring cyclohexanehexol (myo-, scyllo-, muco-, neo-, and D-chiro-Inositol) or its derivatives (L-chiro-, allo-, epi, cis-Inositol)[1,2] Inositols were first identified in 1850 from muscle cells by Johann Joseph Scchere, a German physician and chemist, and named it from the Greek terms [ἰς (is, in-, "sinew, fiber"), -ose (indicating a carbohydrate), -ite ("ester"), -ol ("an alcohol")] to describe its sugar alcohol configuration[3,4]. Inositols are important components of eukaryotic cell membranes and they are involved in biological signal transduction, osmoregulation, and phosphate storage[1,5,6]. It has received much attention in medicine in recent years as a plant-based supplementation for metabolic syndrome, reproduction, and pregnancy development[7-11]. Myo-inositol (MI) being the most bioavailable and the most popular isoform, it is used in topical, oral, and intravenous (IV) forms for various clinical practices.

To date, it is often used with metformin to treat women with polycystic ovarian syndrome (PCOS). MI has similar biological properties to insulin and is widely used for its insulin-sensitizing property on various tissues, including the ovary[12]. It is mainly catabolized by the kidneys or converted to D-chiro-inositol (DCI) by the NADH-dependent epimerase under insulin stimulation[13,14]. Both MI and DCI increase glucose uptake and conversion to glycogen in cells and reduce the release of free fatty acids from adipocytes[11,14]. Given the intricate link of skin health to hormones and metabolism, it is interesting to explore the possible utility of inositols in dermatology.

Methods

Literature Search

This study was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15]. A primary literature search was conducted with PubMed, Ovid/MEDLINE, and Embase in the Cochrane Library databases on December 20, 2021, without limitation as to dates. Medical Subject Headings (MeSH®) controlled vocabulary, text words, and database-specific wildcards were utilized to develop the search terms.

Study selection and appraisal

All reviewers independently screened all article titles and abstracts to include clinical trials, cohort studies, case-control studies, retrospective analyses, case series, cross-sectional studies, or case reports, written in English, of inositol-related interventions in human subjects in the field of dermatology. Animal studies,

reviews, and articles not written in English or Chinese were excluded. Subsequently identified studies were then subjected to full-text review. Rationales for exclusion and article appraisals were recorded at every stage. The final decision on study selection was reached by discussion. References of included and excluded studies were reviewed for potential studies not identified through the initial search strategy and added according to the criteria mentioned above.

Data extraction and analysis

Included studies were summarized using a data extraction form. Authors were contacted for missing data. Studies were graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. Bias risk and methodological qualities were assessed using the Risk of Bias tool for randomized controlled trials, and the Newcastle-Ottawa Scale (NOS) for observational studies. Results of included studies were described in synthesized narratives and are presented in **table I**.

Table I: Recommended use of systemic inositol.

Study	Study type	Subject	Regime	Trial duration (month)	Route	Primary outcome measure Results	AEs
Hyperandrogenism – acne, hirsutism							
Fruzzetti, 2017[32]	RCT	50 PCOS women (inositol: 24, metformin: 22) + 30 healthy controls	MI, 4g, daily plus folic acid, 400mcg, daily; or metformin, 1500mg, daily	6	Oral	On patient-self assessment, 1. 20% of inositol group and 12% of metformin group felt a slight improvement in hirsutism, 0% and 12% reported worsening, the remaining reported no change 2. 38% of inositol group and 43% of metformin group felt a slight improvement in acne, 12% and 7% reported worsening, the remaining reported no change	None
Pezza, 2015	RCT	100 PCOS women with acne	Inositol, 2g, BID (50) or placebo (50)	6	Oral	Decreased number of papulopustular lesions	None
Fabbrocini, 2017	Uncontrolled clinical trial	40 women with adult female acne	4% MI and 1% trehalose-loaded liposomes, overnight every other day	2	Peel-off facial mask	1.Significantly reduced mean count of comedones (-3.9), papule (-6.1), pustule (-2.0), and nodular (-0.5) lesion (P<0.001) 2.GAGS scale scores reduced from 16.8±5.3 to 9.8±4.6 (P<0.001) 3.Sebutape score decreased from 3.4±0.6 to 1.8±0.2 (P<0.001)	None
Minozzi, 2008	Uncontrolled clinical trial	46 women with mild to moderate hirsutism	MI, 2g, BID	6	Oral	Hirsutism score decreased by -2.3±0.9 (P<0.001)	None
Advani, 2020	Uncontrolled clinical trial	Obese (35) or lean (16) PCOS women*	Trazer F Forte™, BID: Inositol (MI:DCI) 600 mg, NAC 300mg, Biotin 5mg, 10% Lycopene 5mg, Chromium picolinate 200 mcg, Folic Acid 120 mcg, Vitamin D 400 IU	3	Oral tablet	In the obese and lean group, 1.Acne score scores -10.05 (P<0.001) and -4.38 (P<0.01), respectively 2.Hirsutism score scores -0.45 (P<0.01) and -0.25 (P<0.05), respectively	None
Ramanan, 2020	Uncontrolled clinical trial	32 females with mild-to-moderate acne and hirsutism	Tracnil™, BID: MI, 2g; folic acid 1mg, vit D3 1000IU	6	Oral powder sachets	1.IGA scores on acne reduced from 4.34±0.33 to 1.3±0.14 by Weeks 24 2.mFGHS reduced by 8.6, 7.4, and 5.8 by Weeks 4, 12, and 24, respectively	Mild GID in some patients
Inflammatory dermatosis – atopic dermatitis, seborrheic dermatitis, hidradenitis suppurativa, psoriasis							
Allan, 2004	Crossover RCT	Patients on lithium who developed chronic plaque psoriasis (15) or patients not on lithium with psoriasis (8)	Inositol, 6g, daily	2.5	Oral	1. Patients on lithium: PASI scores -1.7 in the inositol group compared to +1.9 in the placebo group (P>0.05) 2. Patients not on lithium: PASI scores +0.7 in the inositol group compared to -0.75 in the placebo group (P=0.015)	None
Owczarczyk-Saczonek, 2021	RCT	46 patients with mild plaque psoriasis (PASI<10, BSA<10%); 10 healthy controls	1% (B) or 0.25% (C) DCI, 1 FTU, BID, or placebo applied to three different psoriatic plaques	1.5	Topical cream	1.VAS scores reduced by 22% and 33% in the B and C group; and 23% in the placebo group (P<0.05) 2.PSI scores reduced by 30% and 45% in the B and C group; and 28% in the placebo group (P<0.05)	Not reported

►►

Study	Study type	Subject	Regime	Trial duration (month)	Route	Primary outcome measure Results	AEs
Dall' Oglio, 2017	Uncontrolled clinical trial	25 patients with mild-to-moderate SD	GPI, piroctone olamine, lactoferrin, and Aloe vera, BID	1.5	Topical gel	1. Excellent response (IGA = 4) in 47.9% of patients and no case of worsening (IGA = 0) 2. Significant reduction in desquamation, erythema, and pruritus (P<0.001)	None
Donna-rumma, 2020	RCT	20 patients with HS	Antibiotics with (10) or without (10) MI 2g, liposomal magnesium and folic acid, BID	6	Oral	Reduction of Sartorius scores from 38.3±7.5 to 27.3±13.53 (P<0.04), compared to non-significant reduction in the control group	None
Vascular and circulation – Raynaud's disease, ischemic ulcer, calciphylaxis							
Sunderland, 1987	RCT	23 patients with primary RP	Hexopal ®, 4g, daily (11) or placebo (12)	3	Oral	1. Significantly reduced frequency (P=0.032) and duration (P=0.058) of attack in Hexopal group; non-significant increase in duration of attack in placebo group 2. Higher subjective improvement in the Hexopal group vs placebo group (80% versus 50%)	None
Ring, 1981	Uncontrolled clinical trial	18 patients with secondary RP	Hexopal ®, 1g, QID	9	Oral suspension or tablet	Progressive improvement in TG and RTG, with the latter reaching significance at Weeks 36 (P<0.05)	None
Holti, 1979	Uncontrolled clinical trial	30 patients with primary (14) or secondary (16) RP	Hexopal ®, 4g, daily	3	Oral	1.Significantly higher "on arrival" finger temperatures at Weeks 4, 8, and 12 with no difference in "after heating" temperatures (P<0.01) 2.Non-significantly lower thermal clearance readings (indicates more rapid blood flow) towards Weeks 12 3.Significantly longer time to induce RP at Weeks 4, 8, and 12 (P<0.001)	None
Mishima, 1997	RCT	227 patients with ischemic ulcers	Inositol, 400mg, TID (116) or pyridinol-carbamate, 500mg, TID (111)	1-1.5	Oral	57% and 49% of the patients achieved clinical improvement in the inositol group at Weeks 4 and 6 respectively, compared to 50% and 68% in the pyridinol-carbamate group	Mild AEs (10), severe 6.8% slight to moderate GID 1.3% severe GID requiring termination
Branden-burg, 2019	Uncontrolled clinical trial	14 HD patients with calciphylaxis	SNF472, 7mg/kg, TIW	3	Intra-venous infusion	1. BWAT improved from 33.6±9.6 to 25.6±7.3 (P<0.001) 2.Reduction in pain VAS from 71.8±29.2 mm to 48.1±28.6 mm (P=0.015) 3.Wound-QoL improved from 2.44±0.89 to 1.54±0.90 (P=0.003)	4 (28.6%): unspe-cified
Perelló, 2018	RCT	8 HD patients with calciphylaxis; 20 healthy volunteers	SNF472, 9mg/kg, every 48 hours	1.5	Intra-venous infusion	No significant change in serum calcium levels	Paraes-thesia oral (1), moderate HTN (1)
Psychodermatoses – skin picking, trichotillomania							
Seedat, 2001	Case series	3 patients with trichotillomania and compulsive skin picking	Inositol, 6g, TID (primary treatment in two and adjunct to SRI in one)	2-3	Oral powder dissolved in water or juice	Two patients reported a CGI-I score of 2 (much improved), and one (adjunct to SRI) reported CGI-I of 1 (very much improved)	Mild GID (2) and headache (1)
Neoplasm							
Khurana, 2019	Case report	A patient with stage IVB melanoma	IP6+inositol (800 mg/220 mg), 5 tablets, BID	24	Oral tablets	Restaging scans showed significant improvement after 6 months, complete clinical and radiological remission after 2 years	None

AEs: adverse events; PCOS: polycystic ovarian syndrome; MI: myo-Inositol; DCI: d-chiro-Inositol; BID: twice a day; FTU: fingertip unit; PSI: plaque severity index; VAS: visual analogue scale; TH: trehalose; GAGS: global acne grading system; TIW: thrice a week; BWAT: Bates-Jensen Wound Assessment Tool; QoL: quality of life; HD: hemodialysis; SEs: side effects; PASI: psoriasis area and severity index; TID: thrice a day; GID: gastrointestinal disturbance; CGI-I: clinical global impressions-improvement scale; IP6: inositol hexaphosphate; mCS: modified Cook's scale; mFGHS: modified Ferriman-Gallwey hirsutism score; SD: seborrheic dermatitis; GPI: glycero-phospho-Inositol; IGA: investigator global assessment; HS: hidradenitis suppurativa; RP: Raynaud's disease; (R)TG: (reactive) therogradient [temperature difference between the phalanges and the dorsum of the hand]; HTN: hypertension; SRI: serotonin reuptake inhibitor; Hexopal ®: inositol nicotinate.
*Obese/overweight: BMI >23 non-obese/lean: BMI ≤23

Results

Literature search

The literature search yielded 1181 non-duplicate articles. After title and abstract screening, 280 articles met the criteria for inclusion. These articles were subjected to full-text screening and 17 studies were included in this systematic review as depicted by the PRISMA flow diagram (**Figure 1**). This included eight randomized controlled trials, eight uncontrolled trials, and two case reports.

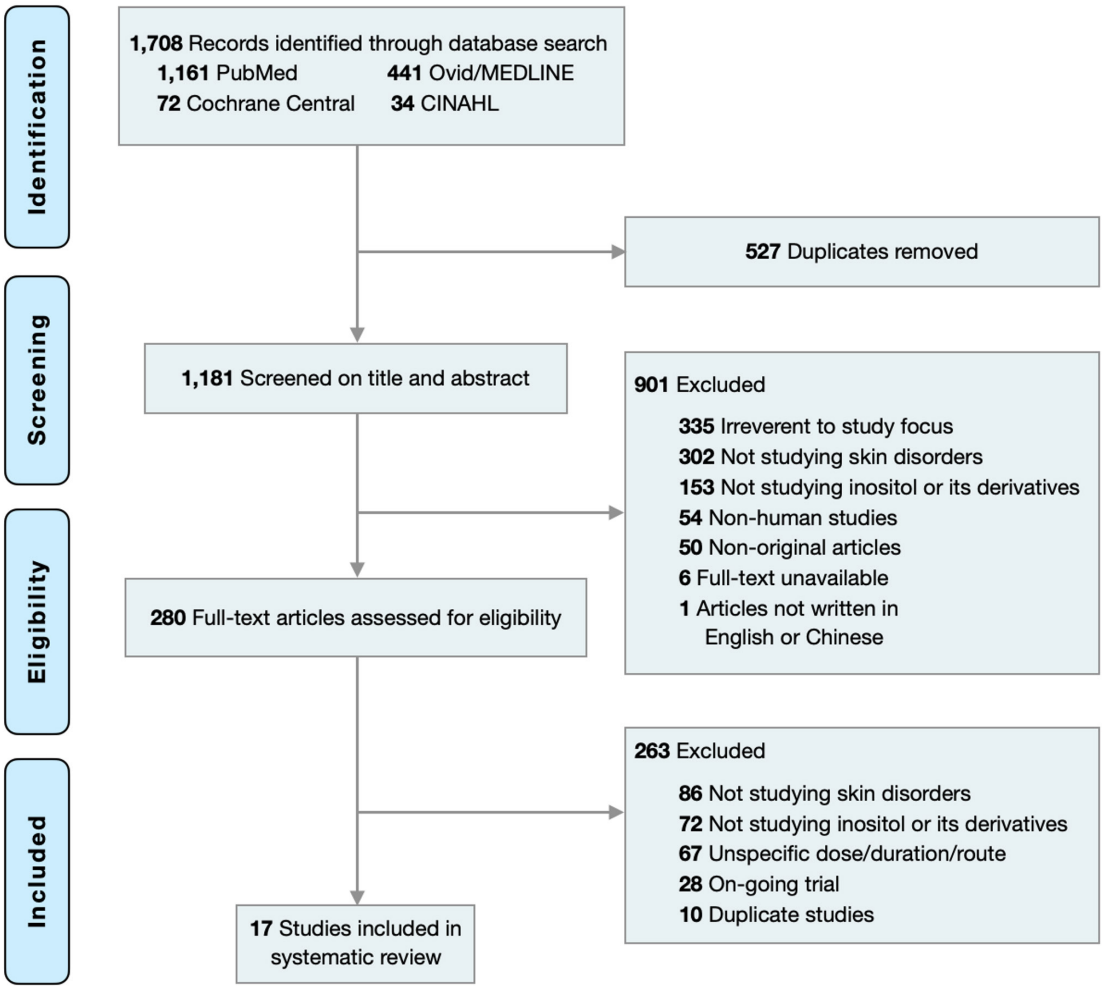
Inositol in dermatology

This review highlighted the existing utilities of inositol in a wide range of skin diseases with various mechanisms of pathogenesis. Inositol is thought of as an insulin-mimetic through multiple modes of action. MI promotes GLUT4 translocation to the plasma membrane, while DCI facilitates glycogen synthesis, enhances insulin signal transduction, and boosts major enzymes in the Krebs cycle to increase glucose utilization and adenosine triphosphate (ATP) production[10,11,13,16-18]. MI also reduces the release of free fatty acids, which promotes a pro-inflammatory state, from adipose tissue, decreases reactive oxygen species (ROS), and reduces white blood cell recruitment[17,19-22]. Given the gut-skin connection, inositol's effects make it a promising therapy to treat cutaneous disorders. Below we further discuss the mechanism and utility of inositol according to clinical subcategories

Hyperandrogenism – acne, hirsutism

At the ovarian level, MI may indirectly increase aromatase activity by follicular stimulating hormone (FSH) modulation. On the other hand, DCI-based second messengers regulate androgen production through the cytochrome P450 system[18,23-25]. Simultaneous alterations in hormonal balance and inflammatory cytokines synergistically improve acne in PCOS women and explain its efficacy in diseases arising from either mechanism. It is hypothesized that besides their individual effects, the ratio of MI and DCI determines the balance of steroidogenesis. Higher

Figure 1: PRISMA flowchart for study selection.



MI:DCI ratios increase estrogen secretion, and lower MI:DCI ratios result in a hyperandrogenic state. Therefore, some research used combined inositol with MI:DCI ratios ranging from 10:1 to 100:1 to address the state of hyperandrogenism such as acne and hirsutism with or without concomitant PCOS[26].

Acne

Acne arises from the interplay among sebaceous glands, *Propionibacterium acnes*, and sex hormones[27-31]. Proposed as an additive insulin sensitizer in women with PCOS, inositol has been found to reduce acne of all stages. Fruzzetti et al[32] and Pezza et al[33] assessed the effect of oral inositol on acne severity in 25 and 50 PCOS females, respectively. Thirty-eight percent of patients in the first study reported improvement in acne symptoms, and the latter found decreased numbers of papulopustular lesions. Interestingly, although these PCOS women had a higher average testosterone level, the former study found no change in the androgen levels Pezza's study reported a decrease in serum dehydroepiandrosterone (DHEAS) concentration. Another study on PCOS women with normal (≤23) or high (>23) body mass index (BMI) revealed a larger decrease in acne scores in overweight or obese subjects compared to lean individuals (-10.05 versus -4.38)[34]. Both groups achieve significant acne clearance within a 12-week course of combined inositol 600mg, twice a day. It is likely that inositol clears acneiform eruptions through multiple mechanisms apart from hormonal regulation. Fabbrocini et al[35] reported a 45-69% reduction in mean acne counts in women with adult female acne and no endocrine abnormalities after 60 days of 4% MI peel-off mask application. In addition, Ramanan et al,[36] after excluding patients with comorbid endocrine and metabolic diseases, revealed a significant reduction on the modified Cook's scale from 4.34 ± 0.33 to 1.3 ± 0.17 after 24 weeks of MI with 2g MI twice daily.

Hirsutism

Hirsutism is the excessive male-pattern hair growth in women. It affects 5-10% of women, depending on age, menopausal status, and race[37]. About 50% of cases are idiopathic while the other half is associated with PCOS (OR = 2.22 [1.30-3.81] or other sex hormones (OR = 1.78 [1.00-3.18])[38,39]. Similarly, PCOS women with hirsutism respond to Inositol, despite to a lesser degree than acne[32,34]. Minozzi, Andrea, and Unfer[40] conducted an uncontrolled clinical trial in hirsute women with or without PCOS using MI 2g, twice a day, for 6 months. The authors found a significant decrease in hirsutism scores (–2.3 ± 0.9, p< 0.001) and total androgens (–13 ± 2.6, p< 0.002) from the baseline. Likewise, the modified Ferriman-Gallwey hirsutism score (mFGHS) decreased from 10 to 5.8 in the study by Ramanan et al[36] using the same regime. Besides, 60% less of patients were complaining of hair loss at the end of the study.

Inflammatory dermatosis – psoriasis, seborrheic dermatitis, hidradenitis suppurativa

Psoriasis

Psoriasis is a chronic inflammatory dermatoses characterized by IL-23/IL-17 activation and Th17/Treg imbalance[41,42]. First reported in 2004 as a remedy for psoriasis in patients taking lithium, oral Inositol replenished lithium-induced Inositol depletion in psoriatic lesions without decreasing its efficacy in patients treated for bipolar disorders[43]. However, such improvement was not observed in patients taking inositol without lithium, suggesting that the endogenous production of inositol can be easily disturbed[22]. Another group of researchers investigated the effect of 1% or 0.25% d-chiro-Inositol (DCI) on chronic plaque psoriasis. Both concentrations, as well as placebo, showed statistically significant subjective and clinical improvement of psoriasis. It was speculated that placebo-related improvement may be related to the topical vehicle base improving the skin condition. The high-dose DCI showed better biophysical measurements and the low-dose regime had a larger reduction in psoriasis severity on clinical evaluation[22]. The contradictory results in these two studies may arise from different patient characteristics, routes of administration, or other non-specific mechanism. More research is required to understand the role of inositol in psoriasis treatment.

Seborrheic dermatitis

Seborrheic dermatitis (SD) affects people of all ages but is most common in infants and in adults aged 30-60 years. The adult form is often precipitated by stress or sleep deprivation and its pathogenesis is likely multifactorial, including hormone levels, skin flora composition, fatty acid metabolism, and neurogenic factors[44]. Dall' Oglio et al[45] applied a new cosmetic topical gel containing glycerol-phospho-Inositol (GPI) to 25 patients with mild-to-moderate facial SD. They found a significant reduction on the investigator global assessment scale and an excellent response (>80% improvement) was reported in near 50% of the cases. Although it is reasonable that inositol improves SD through hormonal and metabolic regulation, there is limited data on this hypothesis. Besides, it was unclear whether the effect was due to GPI or other ingredients in the product.

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a relapsing-remitting inflammatory dermatoses characterized by painful nodules, abscesses, and sinus tract formation[46]. It can cause significant disfigurement due to fibrosis and scarring. Interactions between innate immunity and skin microbiota as well as genetic factors have all been linked to HS development[47]. Donnarumma and colleagues performed a randomized controlled trial to estimate the effectiveness of oral MI (2g daily) supplementation. The average Sartorious Score in the experimental group decreased from 38.3±7.75 to 27.3±8.02 (p <0.04), while

the control group showed a reduction from 38.4±7.88 to 31.1±8.02 (p =0.55). There were no similar studies found on HS treatment with inositol.

Vascular and circulation – Raynaud phenomenon, calciphylaxis

Hexopal, or inositol nicotinate, has both immediate and delayed impacts on distal perfusion. Holti et al[48] found that there was a trend toward further improvement in RP patients at[12] weeks of treatment, suggesting other mechanisms such as enhanced fibrinolysis of Hexopal, besides vessel dilation.

Raynaud phenomenon

Raynaud phenomenon (RP) is a complex entity due to abnormal vascular reactions to temperatures. It can be a primary disease or secondary to other connective tissue diseases. Treatment includes vasodilators such as nitric oxide, calcium channel blockers, and alpha-blockers[49,50]. Three studies conducted during 1979-1987 used Hexopal® in patients with primary or secondary RP. Hexopal (inositol nicotinate) is a compound made of inositol and niacin (vitamin B3). Although niacin is the major active ingredient, the inositol component may reduce side effects from nicotinic acid alone and facilitate vasodilation through the $Ca2^{+}$-dependent phosphatidylinositol 4,5-bisphosphate (PIP2) signaling pathway[51]. No adverse event associated with Hexopal® was reported in these studies.

Calcinosis cutis

Calciphylaxis is a rare, life-threatening complication of end-stage renal disease. Its pathophysiology is still poorly understood, but occlusion of microvessels in the dermis and subcutis is frequently observed, resulting in painful necrotic skin ulcers[52]. Sodium thiosulfate, bisphosphonate, and hyperbaric oxygen therapy are the mainstay treatment, where none of above is approved by the FDA. SNF472, an intravenous preparation of myo-inositol hexaphosphate (HM), has received much attention as a crystallization inhibitor. In the phase 1 trial by Perelló and colleagues, they found a dose-dependent decrease in serum ionized calcium levels in healthy individuals while no significant changes were observed in hemodialysis patients[53]. A follow-up phase 2 open-label, single-arm study, however, showed significant improvement in wound healing and pain scores. One study used 2% HM cream to prevent dystrophic calcinosis cutis in 14 male Wistar rats. The investigators induced plaque formation with 0.1% $KMnO_4$ and found a significant reduction in plaque size and weight[54]. Supplementing HM during hemodialysis hypothetically replenishes endogenous crystallization inhibitor phytate and prevents calciphylaxis. Overall, HM may be a potential treatment for calcinosis cutis, whose management is often frustrating.

Psychodermatoses – skin picking, trichotillomania

Inositol is an important component of neuronal cells as well. Hydrolysis of phosphoinositides (PI) is the first step of signal transduction for multiple neurotransmitters. MI regenerates hydrolyzed PI, making it an emerging therapeutic option for psychiatric disorders like depression and the obsessive-compulsive disorder (OCD) spectrum[55,56].

A case series by Seedat S, Stein DJ, and Harvey BH reported successful treatment of refractory trichotillomania and compulsive skin picking with inositol[57]. Inositol has been shown to improve anxiety, depression, and obsessive-compulsive disorder.58 These three patients were treated with a total daily dose of 18g inositol for 8-12 weeks. They reported noticeable improvement in mood and control over their compulsive behaviors. Although the dosage used in this series was much higher than that for other cutaneous disorders, side effects were mild and well-tolerated. Of note, two of them had inositol as primary treatment while one had inositol as an adjunct to a serotonin-reuptake inhibitor (SRI). Interestingly, adjunct treatment with SRI led to "very much improved" symptoms compared to "much improved" symptoms with sole inositol treatment based on CGI-I severity scores.

Neoplasm – melanoma

MI has been shown to modulate both PI3K/AKT and Wnt/β-catenin pathways.59,60 It may also prevent insulin growth factor-1 (IGF-1) receptor-mediated tumor growth by decreasing insulin resistance[61]. Trials on lung and breast cancer chemoprevention or treatment with MI have been reported with promising results[62,63].

Significant inhibition of melanoma line HTB68 by inositol hexaphosphonate (IP6) was first reported in 2006.64 It was hypothesized that IP6 exerts its anti-proliferative effect through the regulation of apoptosis and angiogenesis. IP6's anti-proliferative effect was supported by another *in vitro* study done by Schneider and colleagues.65 An interesting case report of a stage IV melanoma successfully treated with IP6+inositol (800 mg/220 mg) was published in 2019. The patient had had a diagnosis of stage IIIc melanoma on the left foot with in-transit metastasis to the left shin. One year after, he presented with a new *BRAF V600E* mutant stage IVB melanoma on the left medial thigh. He received a total dose of 8g IP6 and 2.2g inositol daily for 2 years when complete clinical and radiological remission was achieved. He continued with the regime with no signs of relapse nor side effect attributable to the treatment[66]. Nevertheless, although inositol has been shown to inhibit the proliferation of many types of cancer, this is the only report on melanoma in humans so far.

Other Adverse Effects (AEs)

The LD50 of oral MI is 1000mg/kg in mice, which is way below the usual therapeutic ranges of 2-6g daily[67]. Most commonly reported side effects were gastrointestinal disturbance including gastritis and vomiting (14), perioral

paresthesia (1), headache (1), moderate hypertension (1), and four cases were non-specified. Although uncommonly administered, limited case studies support the safety of inositol even at a very high dose of 18g per day, and side effects, if any, are usually mild. In the 570 patients reviewed in this article, only 21 patients developed an adverse reaction to inositol. The most common complaint is gastrointestinal disturbance including gastritis and vomiting (14). Others include perioral paraesthesia (1), headache (1), moderate hypertension (1), and non-specified in four cases. It was reported that psychiatric patients can have some mild neurological discomfort including headaches seen in one of the cases in the OCD series[68]. These side effects could be ameliorated by altering the pharmaceutical form and using lower doses[69].

There are a few limitations in this review, the exact composition and dosing of inositol in each study varied significantly. Isoforms used included MI, DCI, GPI, Hexopal, SNF472, and IP6, and the dosage ranged from 600mg to 18g/day over 4 weeks to more than 3 years. There was significant heterogeneity in the quality and varied outcome assessment presented from available studies. In addition, all RCT had small sample sizes and reports on inflammatory dermatoses, psychodermatoses, and skin neoplasms were limited.

In conclusion, inositol is a promising natural ingredient with anti-androgen, anti-inflammatory, anti-cancer, and many other mechanisms of action. It is proven to be effective as an alternative treatment for a wide range of dermatological diseases with very few side effects. Although data on its long-term safety after 2-6 months was limited, increasing tolerance with continual application and articles reporting extended use over 2 years indicated inositol is suitable for long-term maintenance therapy. Dermatologists should consider including oral inositol as a combination therapy in their medication arsenal given its promising results and good tolerability.

Funding

The authors did not receive support from any organization for the submitted work.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Availability of data and material

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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