



Therapeutic Crossroads of Diabetes-Related Skin Disorders: Unveiling Mechanistic Pathways and the Ethnobotanical Promise of Bioactive Remedies

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KEYWORDS

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ABSTRACT:

Introduction: Cutaneous consequences of diabetes mellitus, ranging from acanthosis nigricans to necrobiosis lipoidica, serve as key indications of systemic metabolic and immunological dysregulation. Complex converging mechanisms, such as oxidative endothelium damage, T-cell dysfunction, and hyperinsulinemia-induced IGF-1 receptor activation, are responsible for these manifestations. The objective of this review is to assess the therapeutic potential of particular ethnobotanical bioactives in reducing these processes and to clarify the molecular pathophysiology of these ailments

Objectives: The study elucidates the molecular interplay behind diabetic dermatopathies and critically analyzes the therapeutic efficacy of ethnobotanical bioactives in bridging the gap between ancestral medical knowledge and modern precision treatments.

Methods: To consolidate information linking diabetic dermatopathology and phytopharmacology, we did a comprehensive assessment of the literature across major biological databases (PubMed, Scopus, and Web of Science). The study focused on the bioactive profiles of *Trigonella foenum-graecum*, *Glycyrrhiza glabra*, *Mahonia aquifolium*, and *Centella asiatica*, specifically looking at their molecular interactions with inflammatory and metabolic signaling cascades.

Results: The investigation revealed that several key phytochemicals, such as certain flavonoids, saponins, and terpenoids, have powerful biological actions that directly counteract diabetic skin disease. These agents enhanced insulin sensitivity and reduced cytokine storms by inhibiting JAK-STAT and NF- κ B signaling pathways. Furthermore, these bioactives stimulated skin regeneration and reduced oxidative stress, addressing the underlying causes of endothelial dysfunction in diabetic dermatopathy.

Conclusions: Ethnobotanical agents represent a scientifically validated, multi-targeted therapeutic strategy for managing diabetic cutaneous complications. By combining ancestral pharmacological knowledge with modern molecular insights, these bioactive medicines provide a fresh, integrated approach to dermatologic treatment, justifying their transition from traditional use to evidence-based clinical application in the diabetic community.



1. Introduction

The skin, long thought to reflect interior imbalances, is now being studied as a sentinel of systemic disease. Diabetes mellitus, a global metabolic epidemic, causes the skin to exhibit the obvious scars of chronic hyperglycemia while also revealing the hidden intricacies of oxidative stress, immunological dysfunction, and vascular fragility. Skin issues impact more than half of diabetic patients globally, although they are not overlooked in mainstream endocrinology and dermatology[1-2]. These manifestations, ranging from acanthosis nigricans to necrobiosis lipoidica, are more than just minor issues; they represent early warning indicators of deeper systemic problems. In contrast, whereas Western medicine has typically relied on focused medication, these methods frequently fail to address the complex, diverse character of diabetes-related dermatoses[3-4]. Standard methods focus on single symptoms--reducing inflammation, lowering glycemic load, or modulating the immune system--but rarely address the interaction of underlying processes that produce chronic skin harm. When contrasted with traditional medical systems, particularly Ayurvedic, Chinese, and African ethnomedical approaches, the skin is considered as both a mirror and an extension of systemic health[5]. In recent years, the tide has started to turn. Plant-based medicines, which had been disregarded for a long time, are finally gaining traction, thanks to a rising foundation of empirical evidence and molecular validation. Phytochemicals, such as flavonoids, alkaloids, terpenoids, and polyphenols, have been demonstrated to interfere with critical inflammatory and metabolic cascades involved in diabetic skin problems, including the NF- κ B, JAK-STAT, IGF-1R, and AGE-RAGE signalling pathways. Unlike single-targeted medications, many ethnobotanical extracts have "multi-hit" effects, which reduce inflammation, restore barrier function, increase angiogenesis, and improve insulin sensitivity[6-7]. For example, *Trigonella phonium-graecum* (fenugreek) lowers the glycemic index while simultaneously promoting epidermal regeneration via 4-hydroxyisoleucine. *Glycyrrhiza glabra* (licorice) protects the skin from oxidative damage by reducing the cytokine storm. These dual-action therapies provide a therapeutic rationale that modern pharmacology is only now beginning to understand[8]. Regional

epidemiology data emphasize the necessity for a comprehensive approach. In India alone, up to 82% of diabetic patients have skin problems, which are frequently resistant to traditional treatments. Southeast Asia exhibits this pattern of symptoms, but high-income countries are reporting rising prevalence of diabetic dermopathy and psoriasis among metabolically unstable people[9-10]. These changes highlight the need to broaden the therapeutic net, not just in terms of innovation, but also in terms of implementing culturally rooted, evidence-based treatments. This review bridges the gap between traditional plant knowledge and current scientific findings. By identifying the genetic foundation of eight primary diabetes-related skin disorders and combining them with phytochemical therapies, we want to establish a therapeutic crossroads where indigenous remedies meet molecular medicine and skin healing occurs from within.

2. Epidemiology of skin diseases in diabetes mellitus

Skin problems are becoming recognized as an important component of diabetes mellitus, affecting more than half of the global population. It is believed that 51-97% of diabetic patients experience skin symptoms, with fungal infections, diabetic dermopathy, and xerosis being the most prevalent. These skin issues are frequently caused by a complicated interplay of microvascular damage, immunological dysfunction, and metabolic imbalance. Fungal infections affect one-third of diabetes patients globally, emphasizing the importance of poor barrier function and chronic hyperglycemia in the development of skin fragility[11-14]. Diabetes is becoming increasingly common throughout Asia, particularly in Southeast Asia, as a result of urbanization and lifestyle changes. India, home to around 9% of the adult diabetic population, provides an intriguing case study. Regional studies have found that up to 82% of Indian diabetic patients had one or more skin disorders. The most common conditions include xerosis, infection, dermopathy, and acanthosis nigricans. Notably, acanthosis nigricans is strongly associated with insulin resistance and metabolic syndrome, particularly in overweight individuals. Diabetic dermopathy, while frequently underreported, can suggest early microangiopathic problems[15-18]. The economic cost of addressing skin diseases in diabetic people is not insignificant. Estimates range



from \$100 to \$500 per patient worldwide, with an average annual expenditure of Rs.2,500-7,000 in India. Despite their clinical and economic importance, skin problems remain underrepresented in national diabetes management guidelines. To address this often overlooked facet of diabetic care, a coordinated effort toward epidemiological surveillance, early diagnosis, and integrated skin-health management is required [19-20].

3. Pathogenic Mechanisms and Ethnobotanical Interventions

Table 1 Burden of skin disorders in diabetic patients by region

Region	Diabetes Prevalence	Skin Disorder Burden in Diabetics	Common Manifestations	Estimated Cost per Year
Global	~9.3% adults (463 million) [21]	51%–97% affected; infections in ~21–32% [21]	Fungal infections, diabetic dermopathy, xerosis, pruritus [21]	~\$100–400 per patient [22]; >\$30B globally [22]
Asia (SEA)	High and rising [21]	Similar to global, with regional variances [21]	High fungal infections, AN; varied prevalence across countries [21]	~\$120–500 per patient [24]
India	~9% adults (77–88 million cases) [21]	61%–82% of diabetics show skin lesions [21]	Xerosis (44%), infections (~31–38%), dermopathy (8–36%), AN (~12%) [21]	INR 2,500–7,000/year per patient [23]

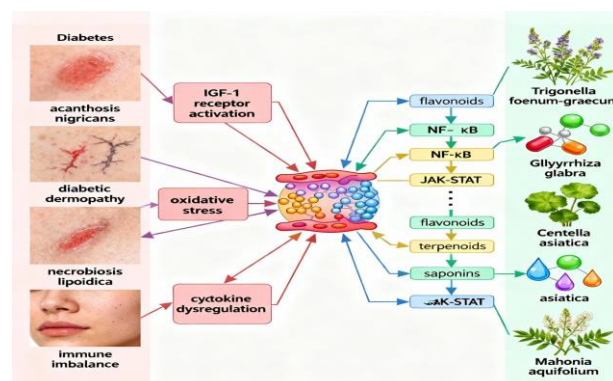


Fig.1 Schematic illustration of the interrelated molecular pathways behind diabetes-related skin diseases and the ethnobotanical treatments. Several dermatologic symptoms, including acanthosis nigricans, diabetic dermopathy, and necrobiosis lipoidica, are caused by central pathogenic pathways such as IGF-1 receptor activation, oxidative stress, cytokine dysregulation, and immunological imbalance. Ethnobotanical bioactive compounds from plants such as Trigonella foenum-graecum, Glycyrrhiza glabra, Centella asiatica, and Mahonia aquifolium modulate inflammatory signaling cascades (NF-κB, JAK-STAT) and metabolic processes to promote skin regeneration and reduce lesions. This comprehensive method identifies possible multi-targeted medicines that bridge traditional medicine and molecular research[25-30].

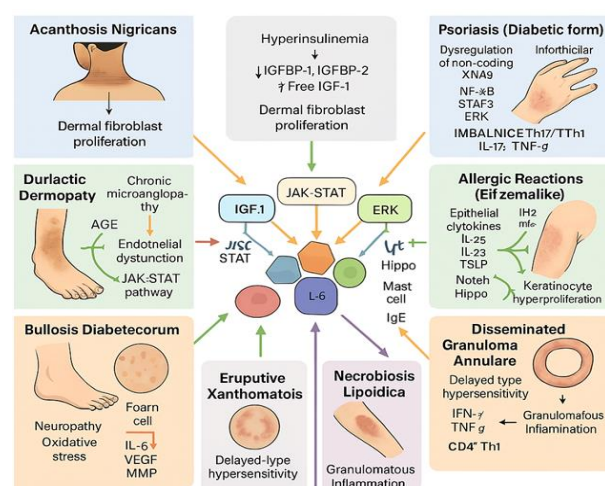


Fig. 2 Integrated Mechanistic Pathways Underlying Eight Diabetes-Associated Skin Disorders[25, 26, 29, 31,32]



This thorough diagram elucidates the molecular and immunological pathways that connect eight diverse skin conditions to diabetes mellitus. The cascade begins with hyperinsulinemia, which stimulates IGF-1 receptor (IGF-1R) signaling while suppressing IGF-binding proteins (IGFBP-1 and IGFBP-2), increasing free IGF-1 levels and driving dermal fibroblast proliferation, a characteristic of acanthosis nigricans (AN[33-34]). In diabetic dermopathy (DD), persistent microangiopathy and AGE buildup disturb endothelial homeostasis and activate JAK-STAT, principally through STAT1/STAT3, resulting in structural deterioration and pigmentation at the dermal-epidermal interface. Diabetes-related psoriasis is caused by altered non-coding RNA regulation, which impacts NF- κ B, STAT3, and ERK pathways. Additionally, the Th17/Th1 cytokine axis (IL-17, TNF- α) promotes chronic keratinocyte hyperproliferation [35-36].

Eczematous lesions are caused by epithelial-derived cytokines (IL-25, IL-33, TSLP), which activate Th2 and Th17 circuits via Notch and Hippo signaling, resulting in IgE-driven mast cell degranulation and allergic inflammation. In bullous diabeticorum (BD), increased oxidative stress, neuropathy, and elevated IL-6, VEGF, and MMPs degrade the extracellular matrix, making the skin prone to blistering[37-38]. Eruptive xanthomatosis (EX) results from lipid dysregulation, in which high triglycerides cause foam cell production and localized macrophage-driven inflammation. Th1-skewed immunity in granuloma annulare (GA) and necrobiosis lipoidica (NLD) causes inflammation, collagen breakdown, and dermal necrobiosis through IFN- γ and TNF- α production [39-40].

Together, these interrelated molecular networks, which include oxidative stress, immunological imbalance, and vascular injury, provide a cohesive pathogenic framework, opening up possibilities for multi-targeted therapeutic approaches in diabetic skin disease treatment.

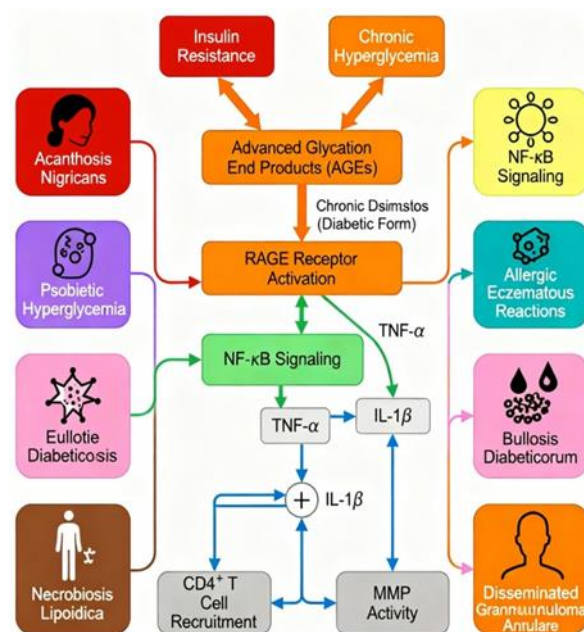


Fig. 3 Integrated molecular pathways linking diabetes mellitus to eight major skin disorders

This diagram depicts the complicated biochemical pathways that connect and drive the development of eight different diabetes-related skin disorders. The schematic begins with insulin resistance and chronic hyperglycemia, both of which are hallmarks of diabetes and contribute to the production of advanced glycation end products. AGEs bind with their receptor (RAGE), leading to downstream signaling processes, including NF- κ B activation [41]. NF- κ B activation increases the transcription of pro-inflammatory cytokines including TNF- α and IL-1 β , creating a self-sustaining inflammatory milieu. Elevated cytokines promote CD4⁺ T cell recruitment and MMP activity, leading to extracellular matrix breakdown and compromised skin structural integrity [42-43].

Table 2 Bridging ancient plant wisdom with modern scientific evidence for therapeutic botanicals used in the treatment of diabetes-related skin conditions

Skin Disorder	Plant Scientific Name	Common Name	Part Used	Ayurvedic Function	Bioactive Molecules	Scientific Mechanism of
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	Name					Action
1. Acanthosis Nigricans[44-47]	<i>Trigonella foenugraecum</i>	Fenugreek	Seeds	Medhya (enhances metabolism)	4-Hydroxyisoleucine, Trigonelline	Enhances insulin sensitivity, reduces keratinocyte overgrowth
	<i>Glycyrrhiza glabra</i>	Licorice	Root	Varnya (skintoner)	Glycyrrhizin, Liquiritin	Antioxidant, reduces inflammation in dermal tissues
	<i>Tanacetum parthenium</i>	Feverfew	Whole plant	Kushthagna (anti-skin disease)	Parthenolide, Flavonoids	Inhibits hyperinsulinemia-mediated IGF-1 activation
	<i>Ginkgo biloba</i>	Maidenhair tree	Leaves	Vatahara (nervine)	Flavonoids, Terpenoids	Enhances circulation, antioxidant, modulates insulin pathways
2. Diabetic Dermopathy[48-51]	<i>Morinda charantia</i>	Bitter melon	Fruit, Seeds	Deepana (digestion enhancer)		Promotes insulin release, antioxidant support for dermal repair
	<i>Anethum graveolens</i>	Dill	Seeds, Leaves	Agnidipana (digestive fire stimulant)		Supports microvascular flow, anti-inflammatory
	<i>Trigonella foenugraecum</i>	Fenugreek	Seeds	Shleshmaha (mucolytic)		Delays carbohydrate absorption, improves insulin response
	<i>Zingiber officinale</i>	Ginger	Rhizome	Pachana (digestive carminative)		Boosts peripheral glucose uptake, reduces inflam



						mation
3. Necrobiosis Lipoidica[52-55]	<i>Bergenia ciliata</i>	Pashanbhedha	Rhizome	Vranashodhana (wound cleanser)	Bergenin, Quercetin	Promotes tissue regeneration, reduces vascular inflammation
	<i>Calendula officinalis</i>	Marigold	Flowers, Leaves	Ropana (wound healer)	Lutein, Kaempferol, Terpenoids	Antioxidant, reduces cytokine-mediated collagen breakdown
	<i>Melaleuca alternifolia</i>	Tea Tree	Leaves (oil)	Kandughna (itch reliever)	Terpinen-4-ol, Cineol	Antibacterial, enhances skin healing, reduces inflammation
	<i>Matricaria chamomilla</i>	Chamomile	Flowers	Shothahara (anti-inflammatory)	Chamazulene, Apigenin	Reduces oxidative stress, supports β -
						cell function
4. Psoriasis[56-59]	<i>Aloe vera</i>	Aloe	Leaf gel	Twachya (skin nourisher)	Acemannan, Anthraquinones	Modulates T-cell activation, reduces keratinocyte proliferation
	<i>Mahonia aquifolium</i>	Oregon grape	Root, Stem	Kushthaghna (skin disease remedy)	Berberine, Flavonoids	Suppresses STAT3, inhibits inflammation and scaling
	<i>Indigo naturalis</i>	Indigo	Leaves	Rakta prasada (blood purifier)	Indirubin, Isatin	Inhibits keratinocyte proliferation, anti-inflammatory
	<i>Capsicum annuum</i>	Red Chili	Fruit	Kandughna (anti-itch)	Capsaicin	Modulates substance P, reduces inflammation and scaling
5.	<i>Aza</i>	Nee	Le	Krim	Azadir	Inhibit



Allergic Reactions[60-63]	<i>dirachta indica</i>	m	av es, Ba rk	ighna (anti micro bial)	achtin, Nimbi n	s histam ine releas e, modul ates immu ne respon se
	<i>Curcuma longa</i>	Tur meri c	Rh izo me	Visha ghna (deto xifier)	Curcu min, BDM C	Inhibit s mast cell degra nulation, anti- inflam mator y
	<i>Ulmus rubra</i>	Slip pery Elm	Inn er Ba rk	Shoth ahara (anti- swell ing)	Mucila ge, Tannin s	Muco protec tive barrier , reduces histam ine- media ted swelli ng
	<i>Isatis tinctoria</i>	Woa d	Le av es	Kand ughn a (anti- itch)	Indiru bin, Trypta nthin	Suppr esses IgE pathw ays, immu ne modul ation
6. Bullosis Diabet	<i>Centella asiatica</i>	Got u kola	Le av es, Ste	Vran a Ropa na	Asiatic oside, Madec assosid	Enhan ces collag en

icorum[64-67]			ms	(wou nd heale r)	e	produ ction, tissue repair
	<i>Vaccinium myrtillus</i>	Bilb erry	Fr uit s, Le av es	Rakta prasa daka (bloo d clean ser)	Antho cyanin s, Flavon oids	Impro ves micro circul ation, antiox idant and woun d healin g
	<i>Pterocarpus marsipium</i>	Vija ysar	Ba rk	Medo ghna (anti- obesi ty)	Pterost ilbene, Marsu psin	Enhan ces glyce mic contro l, suppo rts healin g
	<i>Glycyrrhiza glabra</i>	Lico rice	Ro ots	Varn ya (skin brigh tener)	Glycyr rhetini c acid	Anti- inflam mator y, antimi crobial, woun d protec tor
7. Eruptive Xanthomas[68-71]	<i>Abelmoschus esculentus</i>	Okr a	W hol e Pla nt	Shles hmah ara (slim e reduc er)	Polysa cchari des, Galact uronic acid	Regul ates lipid and glucos e metab olism
	<i>Achyran</i>	Apa mar	W hol	Lekh ana	Alkalo ids,	Anti- lipide



	<i>thes aspera</i>	ga	e Plant	(fat reducer)	Saponins	mic, regulates triglyceride metabolism
	<i>Aegle marmelos</i>	Bael	Leaves	Dipana (digestive)	Marmelosin, Aegelinone	Regulates lipid absorption and metabolism
	<i>Ajuga reptans</i>	Ground pine	Whole Plant	Tridosha Shamak	Linoleic acids, Thymol	Anti-inflammatory, antioxidant, regulates serum triglycerides
8. Granuloma Annulare [72-75]	<i>Melaleuca alternifolia</i>	Tea Tree	Leaves (Oil)	Kandughna (itch reliever)	Terpinen-4-ol, α -terpineol	Antimicrobial, reduces granulomatous inflammation
	<i>Hydrastis canadensis</i>	Golenseal	Root	Rakshodhak (blood purifier)	Berberine, Hydrastine	Modulates IL-12 and TNF- α , antimicrobial
	<i>Anethum graveolens</i>	Dill	Seeds	Deep	Limonene	Anti-

	<i>hum graveolens</i>		Leaves	ana (digestive)	ene, Kaempferol	inflammatory, immunomodulating, skin-soothing
	<i>Foeniculum vulgare</i>	Fennel	Seeds	Tridosha Shamak	Anethole, Coumarins	Antioxidant, reduces histamine response, antimicrobial

4. Discussion

The review investigates the complex relationship between diabetes mellitus and its dermatological symptoms, recasting skin abnormalities as potent indications of underlying metabolic, vascular, and immunological problems. It underlines that these disorders are more than just superficial symptoms, but rather indicate systemic changes that can be used to guide early diagnosis and intervention [76]. Researchers examining diabetes consequences have gained a comparative picture of eight important cutaneous illnesses linked by similar molecular pathways, including NF- κ B, JAK-STAT, and oxidative stress signaling. Mechanistic insights, such as IGF-1R activation in acanthosis nigricans and AGE-RAGE-mediated microangiopathy in diabetic dermopathy, emphasize the systemic unity of these disorders [77-78]. For doctors, the study emphasizes the diagnostic and prognostic value of diabetic skin problems. Traditionally treated as peripheral concerns, these symptoms are frequently used as early warning indicators of poor glucose metabolism and inflammation. Recognizing them as clinical biomarkers



rather than cosmetic issues allows for prompt, preventive treatments. The incorporation of ethnomedicinal techniques, particularly in low-resource communities, emerges as both practical and culturally sensitive, complementing traditional treatment approaches[79-80]. From a translational science standpoint, the debate emphasizes the latent pharmacological potential of medicinal plants like *Trigonella foenum-graecum*, *Glycyrrhiza glabra*, *Centella asiatica*, and *Mahonia aquifolium*. These botanicals, which are high in bioactive substances like as flavonoids and saponins, have multitarget capabilities that control insulin signaling, reduce inflammatory cascades, and protect against oxidative stress. Moving beyond anecdotal evidence, the paper recommends using transcriptomics, network pharmacology, and molecular docking to elucidate the molecular mechanisms[81-83]. Given the increased prevalence of diabetes-related skin problems, particularly in India and Southeast Asia, incorporating established ethnobotanical remedies could give cost-effective, accessible therapeutic options. Finally, this synthesis advocates for combining traditional medical wisdom with new molecular research to reframe cutaneous diabetic symptoms as pathways to comprehensive disease management and precision care.

5. Conclusion

The review emphasizes the skin's critical function as an active communicator of systemic disease, particularly in diabetes mellitus. Far from being a passive surface, it reflects the metabolic, vascular, and immunologic abnormalities that constitute the illness. The synthesis examines eight dermatologic disorders and identifies interrelated pathways (JAK-STAT, NF- κ B, and AGE-RAGE) that link cutaneous symptoms to underlying metabolic abnormalities. This junction provides researchers with opportunities to find shared biological targets, while physicians get a framework for evaluating skin manifestations as early diagnostic indicators of metabolic imbalance. Ethnobotanical agents such as *Trigonella foenum-graecum*, *Glycyrrhiza glabra*, and *Centella asiatica* have emerged as scientifically promising therapies that bridge traditional practice and evidence-based medicine. Integrating molecular insights with approved phytotherapy has the potential to change

diabetic care by improving precision and accessibility. Finally, the skin's interaction with interior disease compels medicine to pay closer attention--and translate its signals into comprehensive healing.

Abbreviations

IGF-1	Insulin-like Growth Factor 1
JAK-STAT	Janus Kinase - Signal Transducer and Activator of Transcription pathway
NF- κ B	Nuclear Factor kappa-light-chain-enhancer of activated B cells
R	Receptor
AGE-RAGE	Advanced Glycation End-product κ Receptor for AGE axis
\$	Currency (context-specific, e.g., dollar)
INR	Indian Rupee
IGFBP-1	Insulin-like Growth Factor Binding Protein 1
IGFBP-2	Insulin-like Growth Factor Binding Protein 2
IGF-1	Insulin-like Growth Factor 1
ERK	Extracellular signal-Regulated Kinase
AGE	Advanced Glycation End-product
IgE	Immunoglobulin E
XNA9	Xenogenic Nucleic Acid 9
STAF3	Signal Transducer and Activator of Transcription Factor 3
Th17	T helper 17 lymphocyte
TTh1	T helper 1 lymphocyte
IL-17	Interleukin 17
TNF-g	Tumor Necrosis Factor gamma
IL-25	Interleukin 25
IL-23	Interleukin 23
TSLP	Thymic Stromal Lymphopoietin
Notch Hippo	Novel TECh Hippo signaling pathway
IFN γ	Interferon gamma
CD4	Cluster of Differentiation 4
Th1	T helper 1 cell
IGF-1	Insulin-like Growth Factor 1
AN	Acanthosis Nigricans
DD	Diabetic Dermopathy
STAT1	Signal Transducer and Activator of Transcription 1



STAT3	Signal Transducer and Activator of Transcription 3
Th17	T helper 17 cell
Th1	T helper 1 cell
IL-17	Interleukin 17
TNF-1 α	Tumor Necrosis Factor alpha
TSLP	Thymic Stromal Lymphopoietin
BD	Bullosis Diabeticorum
(EX)	Eruptive Xanthomatosis
(GA)	Granuloma Annulare
NLD	Necrobiosis Lipoidica
IL-1 β	Interleukin 1 beta
CD4+T	CD4 positive T cell
MMP	Matrix Metalloproteinase
AGEs	Advanced Glycation End-products
BDMC	Bisdemethoxycurcumin
Terpine n-4-ol	Terpinen-4-ol (active terpenoid in tea tree oil)

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Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this article.

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