



Centella asiatica: alternative dry skin therapy in type 2 diabetes mellitus

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ABSTRACT

Submitted: 2020-03-20
Accepted : 2021-03-25

Diabetes mellitus (DM) in Indonesia has rapidly increased during recent years. World Health Organization (WHO) predicted that in 2030, Indonesia would be ranked fourth for the largest DM patients in the world. As the disease progresses, uncontrolled type 2 DM (T2DM) results in dry skin as the most prevalent skin disorder. Despite the prevalence and morbidities that lead to infection, ulcer, gangrene that can lead to amputation when insufficiently treated, dry skin in T2DM has limited therapeutic options. Currently, available therapies for dry skin in T2DM have not considered factors of hyperglycemia and hyperinsulinemia, which disturb skin homeostasis. Nonetheless, in T2DM, there are neuropathy and biostructural changes of the skin which induce dry skin. Alternative herbal medicine, *Centella asiatica* is getting well-known nowadays because of its vast amount of benefits. *Centella asiatica* has been studied for its antioxidant, antidiabetic, anti-inflammation, antiglycation, and neuroprotective activities. Furtherly, these properties may display benefits when introduced to T2DM dry skin therapy. The previous clinical study had shown that topical *C. asiatica* improved dry skin. This clinical study was also supported by *in vitro* studies. Currently, pharmacological profile studies of *C. asiatica* including dosage, toxicity, and safety have been available. This article aimed to review the current literature on the potential of *C. asiatica* as an alternative to treat dry skin in T2DM.

ABSTRAK

Diabetes mellitus (DM) di Indonesia terus meningkat pesat selama beberapa tahun terakhir. World Health Organization (WHO) memperkirakan pada tahun 2030 Indonesia memiliki jumlah penderita terbanyak pada peringkat keempat di dunia. Pada perjalanan penyakit DM tipe 2 (DMT2) yang tidak terkontrol, kelainan kulit kering merupakan salah satu kelainan yang paling sering ditemui. Kulit kering pada DMT2 saat ini memiliki terapi terbatas padahal morbiditasnya tinggi, dapat menyebabkan infeksi, ulkus, dan gangren yang menyebabkan amputasi bila tidak tertangani dengan baik. Terapi yang ada saat ini belum melihat kelainan kulit kering pada DMT2 terjadi karena faktor hiperglikemia dan hiperinsulinemia yang mengganggu keseimbangan homeostasis kulit. Selain itu, pada DMT2, terjadi neuropati dan perubahan biostruktur kulit yang memicu kekeringan kulit. Terapi alternatif herbal, *Centella asiatica* saat ini sedang naik daun karena berbagai manfaatnya. *Centella asiatica* terbukti memiliki aktivitas antioksidan, antidiabetes, antiinflamasi, antiglikasi, dan neuroprotektif yang bermanfaat untuk pengobatan kulit kering pasien DMT2. Penelitian klinis sebelumnya menunjukkan bahwa pemberian *C. asiatica* topikal bermanfaat pada kulit kering yang didukung juga dengan penemuan penelitian *in vitro*. Saat ini sudah ada penelitian farmakologi *C. asiatica* yang meliputi dosis, toksisitas, dan keamanan. Tujuan dari artikel ini adalah untuk mengulas potensi dari *C. asiatica* sebagai terapi alternatif untuk kulit kering pada DMT2.

Keywords:
Centella asiatica;
dry skin; therapy;
type 2 diabetes mellitus;
wound healing;

INTRODUCTION

Diabetes mellitus (DM) in Indonesia has been growing progressively. According to WHO data, Indonesia is predicted to rank fourth in the world by 2030.¹ Diabetes mellitus has cost Indonesia 810 million USD financially and became a national health burden. Patients with DM are projected to spend 2.3 times health expenditure compared to healthy people as its complications increase morbidity and mortality.²

Skin is one of the organs affected by uncontrolled DM. A study by Chatterjee *et al.*³ found that 74% of type 2 DM (T2DM) patients suffered from a skin disorder, mainly dry skin (47%) which can become severe, leading to infection, ulcer, and gangrene. In an earlier stage, dry skin should be sufficiently treated to prevent these complications.³ However, options for treating dry skin of T2DM are still limited. Commonly used therapies for dry skin in T2DM have not accounted for the pathogenesis of T2DM-induced dry skin that involves hyperglycemia and hyperinsulinemia, leading to the disturbance of skin homeostasis. It is believed that neuropathy and biostructural changes of the skin occurred in T2DM, leading to dry skin.

Traditional herbal medicine has been emerging in the last few years. One of which is *Centella asiatica*, local name as *pegagan* in Indonesia or *gotu kula* and Indian pennyworth internationally. *Centella asiatica*, part of the *Apiaceae* family, has been long reputed to provide benefits as antipyretic, diuretic, antibacterial, antiviral, and cognitive enhancement agents. *Centella asiatica* has been studied to clinically improve dry skin in the geriatric population. *Centella asiatica* has also been linked to having antidiabetic properties.^{4,5} In this paper, we aimed to review the current literature on the potential of *C. asiatica* as an alternative to treat dry skin in T2DM.

DISCUSSION

Pathogenesis of dry skin disorder in T2DM

In T2DM, there are changes in the mechanical and functional properties of the skin. These changes will affect the homeostatic environment of the skin, commonly manifesting in dry skin. Unfortunately, dry skin tends to be underdiagnosed or ignored until it progresses into more severe skin disorders such as ulcers or gangrene.⁶

In DM animal models, an imbalance of stratum corneum components was observed. Triglyceride was found to be lower, while ceramide, cholesterol, and fatty acid were found to be higher compared to control. In addition, the study also found that the corneocytes in the stratum corneum increased in thickness and size. In contrast, the basal cell proliferation decreased, resulting in slower metabolism in epidermis.^{7,8}

Skin disorder in DM patients resulted from cellular disturbances initiated by hyperinsulinemia and hyperglycemia. Hyperglycemic condition interrupts corneocyte proliferation.⁹ Furthermore, the dermis also changes in morphology and biochemistry due to the degradation of matrix intracellular and microstructural components. In a study from Mozcar *et al.*¹⁰ biopsy of DM patients skin revealed ultrastructural alteration of fibroblast, collagen, and elastic fiber of dermis. Fibroblasts had increased electron-dense deposits in the cytoplasm and dilated endoplasmic reticulum, collagens were dissociated, and elastic fibers were either fragmented or absent. Collagenase and elastase were also altered, resulting in macromolecular matrix changes.

Dry skin is affected extrinsically and intrinsically by numerous factors. Extrinsic factors include lifestyle (hot bath, alkali base soap, and air conditioning) and environment (UV

radiation, dry wind, cold temperature, and climate change). Intrinsic factors include advanced glycation end-products (AGEs), urination, autonomic neuropathy, sebaceous gland production, barrier function of stratum corneum, and desquamation process.¹¹

High blood glucose pathologically affects skin homeostasis through inhibition of proliferation and migration of keratinocytes, biosynthesis of protein,

inducing apoptosis of endothelial cells, and lowering the synthesis of nitrite oxide. High blood glucose also impairs phagocytosis and is chemotactic of several cells. Based on *in-vitro* studies, high blood glucose disturbed proliferation and differentiation of keratinocytes—nonetheless, hyperglycemia-induced AGEs formation. Several alterations in DM patients are summarized in TABLE 1.¹²

TABLE 1. Skin alteration in DM patients¹³

| Parameter | Alteration in DM patients | References |
|---------------------------|--|--|
| Hydration | Decline Insignificant changes | Sakai, <i>et al.</i> ¹⁴ Seirafi, <i>et al.</i> ¹⁵ |
| Transepidermal water loss | Insignificant changes | Sakai, <i>et al.</i> ¹⁴ |
| Filaggrin | Significant changes | Thyssen, <i>et al.</i> ¹⁶ |
| Barrier integrity | Increment Inflammation Infiltrate | Tellechea, <i>et al.</i> ¹⁷ |
| Epidermal thickness | Insignificant changes Thicker epidermis | Zakharov, <i>et al.</i> ¹⁸ Bertheim, <i>et al.</i> ¹⁹ |

Despite the pathogenesis of dry skin in DM remains unclear, several factors are suspected to play a major role:

Systemic mechanism of dry skin in DM

Polyuria, as a common manifestation in DM patients, increases total body water loss, increasing the skin's susceptibility to dryness.²⁰

Neuropathy in DM patients

Neuropathy in DM patients can affect sensory, motoric, and autonomic pathways. Sensory neuropathy can cause sensibility and thermal sensation loss. Meanwhile, autonomic neuropathy can damage the neurological pathway controlling eccrine and sebaceous glands. The damaged neuron will decrease blood flow leading to atrophy of the glands. Atrophy of eccrine and sebaceous glands will decrease the production of lipid and

sweat; thus, the skin tends to be dry. Dry skin is prominent in areas with eccrine gland only, such as the sole. The decrease in peripheral blood flow will increase the damage in dry skin in DM patients. Neuropathy can manifest independently or simultaneously and can be a precipitating factor to the leg ulcer. Leg ulcers in DM patients are challenging to treat and pose a risk for severe infection, and amputation is a common approach in several cases.^{20,21}

Biophysical changes in stratum corneum

In DM, there are biophysical changes in the stratum corneum caused by a change in lipid concentration, epidermal proliferation and differentiation, natural moisturizing factor (NMF), and aquaporin water channels (AQP3) that compromise the skin moisture network. Nonetheless, the study also showed thickening of the corneocyte

layer in stratum corneum, decrement of the proliferation of the basal cell, and damage to epidermal DNA which is essential for epidermal differentiation. The mentioned factors decrease the metabolism rate of epidermis.^{7,14}

In the study of animal models induced with DM, there was impairment in skin barrier, epidermal turnover rate, corneocytes accumulation, and decrease of lipid concentration. This founding was similar to a study in humans with DM where these conditions predispose to dry skin precipitate aging process in DM.¹⁴

Hydration status

Hydration status in rats with induced hyperglycemia was lower compared to normal rats, although there was an insignificant difference in transepidermal water loss (TEWL) between the two groups.^{8,22} Sakai *et al.*¹⁴ conducted a study comparing hydration status and TEWL in a group of patients with a high level of HbA1c and fasting blood glucose (FBG) and another group with low HbA1c and FBG. The study found that hydration status was significantly lower in the high FBG group, while TEWL was not different significantly. In addition, there was an insignificant increase in TEWL in patients with high HbA1c.¹⁴

Stratum corneum functional capacity in DM patient varied depending on current hyperglycemic state (FBG > 110 mg/dL) and average blood glucose control (HbA1c > 5.8%). In the study by Sakai *et al.*,⁷ DM mice with FBG > 110 mg/dL had lower skin hydration compared to FBG ≤ 110 mg/dL, without difference in TEWL. In patients with HbA1c > 5.8%, the TEWL value is slightly lower compared to HbA1c ≤ 5.8% with no significant difference in skin hydration statistically. The study result showed that skin hydration is influenced by current hyperglycemia (FPG) rather than previous hyperglycemia (HbA1c).¹⁴

Another study in DM patients with FBG > 110 mg/dL and HbA1c > 5.8% showed that stratum corneum hydration and TEWL value were similar to control. However, in this study, there was a significant reduction of sebum and functional changes of the sebaceous gland that might contribute to the development of diabetic skin.¹⁵

Depletion of amino acid and lipid concentration

In the animal model with DM, change was not found in the concentration of amino acid (profilaggrin and filaggrin), but there was a decline of lipid in stratum corneum, mainly triglycerides, compared to normal.^{7,23} Seirafi *et al.*¹⁵ reported a lower concentration of lipid in the forehead of DM patients with high level of HbA1c and FBG compared to patients with low level of HbA1c and FBG. This finding is similar to the study in animal models. Decreased lipid in the skin is suspected to be caused by lipolysis in sebaceous gland in hyperglycemic condition.¹⁵

Decreased proliferation and differentiation of epidermis

Diabetes mellitus influenced the structure, proliferation, and differentiation of the epidermis. In mice induced with DM the epidermis is thinner. In addition, the ratio of proliferating cell nuclear antigen (PCNA) basal cell per total basal cell in epidermis, and DNA concentration in epidermis is lower compared to non-DM. Corneocytes were found to be larger in mice with DM. This phenomenon was caused by the decrease in epidermal turnover rate.^{21,22}

Insulin plays a role in keratinocytes proliferation and differentiation. In a rat model with induced DM and DM patients, there was a decrease in insulin signal transduction which causes a decline in keratinocyte migration, proliferation, and differentiation. These conditions

aggravated dry skin in DM patients by creating squama buildup.^{21,22}

A study by Goyal *et al.*²⁴ stated that dry skin was the earliest and the most prevalent skin abnormality found in DMT1 patients. The clinical observation indicated a decrement of hydration status of stratum corneum and sebaceous gland activity, without significant disturbances in stratum corneum barrier.

Centella asiatica

Definition, phytochemistry, and active compounds

Centella asiatica is a prostate stoloniferous plant from *Apiaceae*

family, commonly known as gotu kola or Indian pennywort in America and Malaysia. In Indonesia, it is called pegagan. Therapeutic use of *C. asiatica* has been documented for thousands of years, mainly in Southeast Asia and Bangladesh, mainly used as antipyretic, diuretic, antibacterial, antiviral, and cognitive enhancement agents. In dermatology, *C. asiatica* is used as a therapy for wound, burn, hypertrophic scar, eczema, Morbus Hansen, psoriasis, and lupus erythematosus. *Centella asiatica* is also used in cosmetic and geriatric due to its antiaging capability through the mediation of collagen type I increase.^{25,26}

TABLE 2. Active compound in *C. asiatica*²⁵

| Group | Active compound |
|-----------|--|
| Terpenoid | Triterpen, asiaticoside, centelloside, madecassoside, brahminosid (saponin glikosida), asiatisentoat acid, centellic acid, centoic acid, madecassic acid, terminolic acid, and betulic acid |
| Terpenoid | β -caryophyllene, trans β -farnesene and germacrene D (sesquiterpen), α -pinene and β -pinene |
| Fenol | Flavonoid: kaempferol, kaempferol-3-o- β -d-glucuronide, castilliferol, quercetin, quercetin-3-o- β -d-glucuronide, castillicetin, apigenin, rutin, luteolin, naringin |
| Fenol | Fenilpropanoid: rosmarinic acid, chlorogenic acid, 3,4-di-o-caffeoyl quinic acid, 1,5-di-o-caffeoyl quinic acid, 3,5-di-o-caffeoyl quinic acid, 4,5-di-caffeoyl quinic acid, isochlorogenic acid |
| Fenol | Tannin: tannin, phlobatannin |

Extract of *C. asiatica* leaves consisted of chemical compounds with many benefits, including antimicrobial, antiinflammation, anticancer, neuroprotective, antioxidant, and wound healing. These benefits have been tested in studies and the bioactive compound has

been identified.²⁷ *Centella asiatica* is rich in active compounds, triterpene fraction; mainly asiaticoside, madecassoside, asiatic acid, and madecassic acid (TABLE 2).²⁵ Furthermore, TABLE 3 displays *C. asiatica* active compound biological properties.²⁸

TABEL 3. Biological properties of *C. asiatica* bioactive compound²⁸

| Bioactive compound | Biological properties |
|--------------------|--|
| Asiatic acid | Enhancing neuroglia formation, increasing wound healing with cuticle cornification, stimulating granulation and gene expression, increasing memory and learning capacity, antinociceptive activity, antiinflammation, acetylcholinesterase inhibition, and antiapoptosis |
| Asiaticoside | Antiinflammation, antioxidant, gene expression change stimulation, wound healing, neuroprotective activity, lessening scar formation, increasing collagen biosynthesis |
| Quercetin | Anti-HIV-1, antiasthma, antibacterial, antihepatotoxin, antihypertension, antiinflammation, antitussive, antiviral, coroner vasodilator, antihypercholesterolemia, inhibitor 5-HT, smooth muscle relaxant, platelet aggregation inhibitor, 3.5-cAMP-phosphodiesterase inhibitor, fatty acid synthesis inhibitor, aldose reductase, protein kinase C inhibitor; decrease capillary vulnerability, antioxidant |
| Quercitrin | Antibacterial, antineoplastic, antihepatotoxic, antiinflammation, antimutagenic, antiviral, diuretic, hemostasis, aldose reductase inhibitor, antioxidant, insect antifeedant, insect phagostimulant, hepatoprotective |
| Kaempferol | AntiHIV-1, antibacterial, antiinflammation, antitussive, antioxidant, Δ^5 -lipoxygenase inhibitor; deiodinase tironin iodinat inhibitor, aldose reductase inhibitor |
| Apigenin | antibacterial, antiulcerative, antispasmodic, diuretic, inhibitor aldose reductase. antihypertensive, antiinflammation, antioxidant, nodulation signal for pea metabiosis, and <i>Rhizobium leguminosarum</i> |
| Luteolin | antiallergy, antibacterial, antifungal, cytotoxic, anti inflammation, antispasmodic, antitussive, antiviral, improve arterial pressure and decrease venous pressure, increasing capillary permeability, enhancing immune system, increasing coronary flow, inhibitor of dihydrocoenzyme I (NADH) oxidase, iodine-induced thyronine deiodinase, and aldose reductase, antiinflammation, antiHIV |
| Naringin | antibacterial, antiinflammation, antiviral, inhibitor aldose reductase, inhibitor anaphylactic cutaneous passive |
| Betulic acid | antineoplastic, cytotoxic, antitubercular, antibacterial |
| α -Pinene | antifungal, antitussive, irritant |
| β -Pinene | antifungal, antitussive, antiinflammation |
| Ascorbic acid | antioxidant, antibacterial, antihypercholesterolemia, inhibition of carcinogen production, stimulating tissue to produce collagen, hematopoietic activity |
| Chlorogenic acid | antioxidant, antineoplastic, cytotoxic, antimutagenic, antiviral, hemostatic, leukopoietic, antimalaria |

Studies reported that asiaticoside, asiatic acid, and madecassic acid are capable of increasing collagen type I. Meanwhile only madecassoside is found to increase collagen type III. In fibroblast culture, fraction of

triterpene in *C. asiatica* stimulates collagen synthesis and contributes in inflammation regulation, normalization of keratocyte hyperproliferation, and maintaining epidermal homeostatic.²⁵

Antioxidant activity

Centella asiatica is reported to have comparable antioxidant activity to rosemary extract, sage extract, vitamin C, and grape seed; Thus, *C. asiatica* has been studied as a natural antioxidant product. However, extraction methods also influence the antioxidant activity of the end-product. For example, when comparing water, ethanol, and light petroleum as extract solvent, ethanol has the highest antioxidant activity, followed by water, then petrolatum. Antioxidant activity in *C. asiatica* comes from hydroperoxide reduction which neutralizes free radicals and/or metallic ion bonds. There are several mechanisms of *C. asiatica* antioxidant activity, some of which eliminate reactive oxygen species (ROS) (quercetin and catechin), inhibition of free radical formation, inhibition of chain breaker activity (p-coumaric acids), and metal binding.²⁸

Leaves of *C. asiatica* contain the highest amount of antioxidant compared to other parts of the plant. Antioxidant activity of *C. asiatica* was mainly from hydroperoxide reduction, inactivation of free radicals, binding to metallic ions, and the combination of the three. Application of 0.2% asiaticoside cream 2 times per day for 7 days in excision type wound scar increased enzymatic and non-enzymatic antioxidant, including superoxide dismutase (35%), catalase (67%), glutathione peroxidase (49%), vitamin E (77%) dan ascorbic acid (36%) in recently grown tissue. There was also a decrease in lipid peroxidase (69%). However, the application for 14 days showed insignificant difference in antioxidant activity compared to control. The study concluded that *asiaticoside* induced antioxidant level in early phase of wound healing.²⁸

Wound healing activity

In wound management, *C. asiatica* extract had been applied in chronic

infection treatment. *Aqueous extracts* formulated in cream and gel were tested in rats to evaluate wound healing effect. It was found that *C. asiatica* accelerated epithelization process and enhanced wound contraction.²⁸ In animal models with scar injected with dexamethasone 0.3 mg/kg, after CAo extract ethanol dose were increased from 1, 2, 4, 8, 16 mg/kg for 14 days, the wound was healed.²⁹ In the recent study in Thammasat University Hospital, DM patients consuming 100 mg asiaticoside extract capsule three times per day showed improvement in wound contracture compared to placebo with no side effects.³⁰ Asiaticoside effects in proliferation human periodontal ligament cell (HPDLs), protein synthesis, and osteogenic differentiation showed increase in periodontal tissue.³¹ In a study by Suwantong *et al.*³², asiaticoside in the form of crude asiaticoside 2% extract (CACE) and pure asiaticoside 40% substances (PAC) were loaded into ultra-fine cellulose acetate fiber mats as topical/transdermal patches and wound dressing. Fiber mats loaded with PAC and CACE exhibited more significant proliferation of fibroblast and production of collagen. These loaded fiber mats were stable for up to 4 months.

Antiinflammatory activity

Asiatic acid and madecassic acid compounds in *C. asiatica* possessed anti-inflammatory effect through inhibition of enzyme (iNOS, cyclooxygenase-2 (COX-2)), interleukin (IL-6, IL-1 β), and expression of cytokine tumor necrosis factor (TNF- α) with downregulation of NF- κ B activity in macrophage cell induced by lipopolysaccharide. In an animal study, asiaticoside inhibited fever and inflammation response triggered by lipopolysaccharide via obstructing the production of TNF- α , IL-6, liver myeloperoxidase activity, expression of COX-2 protein in the brain, and prostaglandin production.²⁸

An in-silico study assessed binding

between *C. asiatica* active compounds and pro-inflammatory cytokines (IL-1 α , IL-1 β , and IL-6). The study also examined the interaction between *C. asiatica* active compounds and anti-inflammatory cytokines (IL-4). The study found that *C. asiatica* active compounds (asiaticoside, termolinic acid, madecassic acid, asiatic acid, batulinic acid, and madasiatic acid) interacted significantly with both proinflammatory cytokines (IL-1 α , IL-1 β , and IL-6) and anti-inflammatory cytokines (IL-4). Madecassic acid, asiaticoside, asiatic acid, madasiatic acid, and terminolic acid inhibit the pro-inflammatory cytokines by binding to receptor active sites of IL-1 β and IL-6. Madecassic acid, terminolic acid, and asiaticoside enhanced anti-inflammatory cytokines by binding to IL4 receptor binding sites.³³

Antiaging activity

In fibroblast cell culture in human dermis, asiaticoside enhances the production of type-1 collagen. Based on this, *C. asiatica* was recommended in hypertrophic scar and keloid treatment. *Centella asiatica* ethanol extract exhibited antipruritic properties. Combination of ethanol extract with 4 herbals (*Curcuma caesia*, *Areca catechu*, *Cinnamon zeylanicum*, dan *Tamarindus indica*) in cream formulation ameliorated skin hydration, sebum concentration, viscoelasticity, and lower melanin content.²⁸ A study by Bylka et al. discussing *C. asiatica* benefit in cosmetology showed that *C. asiatica* is effective in small wound treatment, hypertrophic scars, burn scars, psoriasis, and scleroderma. The mechanism of action was through fibroblast proliferation and collagen synthesis and intracellular fibronectin.

Anticancer activity

Each extract of *C. asiatica* solvent

has an anticancer activity specific to different types of cells. Methanol extract of *C. asiatica* induces apoptosis in breast cancer cells in an *in vitro* study. Water extract of *C. asiatica* triggers apoptosis in tumorigenesis colon in male rat F344. Asiatic acid enhances apoptosis in human SK-MEL-2 melanoma which responds to skin cancer cells and colon cancer SW480 in humans. Asiaticoside increases antitumor vincristine in cancer cell. Methanol extract inhibits the proliferation of human gaster adenocarcinoma (MK-1), human uterus carcinoma (HeLa), and cells colarated to melanoma (B16F10).²⁸

Antidiabetic activity

Ethanol and methanol extract of *C. asiatica* lower blood glucose level significantly to normal level in modeled animal rat diabetes-induced with alloxan.²⁸

Neuroprotective activity

Centella asiatica is a potent antioxidant that exhibits a significant neuroprotective effect against oxidative damage due to aging in rat brains. Asiatic acid enhances oxidative cellular protection in the cerebral cortex. Therefore, *C. asiatica* showed efficacy in neuroprotection and preventing oxidative damage from excessive glutamate exposure. *Centella asiatica* accelerates neuron regeneration through oral medication containing several active fractions. These active fractions support neuron elongation *in vitro* hence improving neuron regeneration.⁴

Antiglycation activity

Active *C. asiatica* compounds showed a beneficial effect if applied topically on the skin for wound healing and chronic vein insufficiency. Maramaldi *et al.*²⁵ researched about purified *C. asiatica*

extract for skin wrinkling and skin protection against UV on human skin explant and human volunteer in a single-blind placebo-controlled study. Antiaging properties observed were skin elasticity, plasticity, and collagen density. Thymine dimerization for DNA protection from UV was observed by immunostaining. Formation of malondialdehyde acts as an indicator for free radical scavenging activity, and expression of interleukin 1 α as a proinflammation indicator observed with enzyme-linked immunosorbent assay (ELISA). This study also measured *C. asiatica* ability *in vitro* in inhibiting carboxymethyl lysine (CML), one of AGEs components, as an indicator for antiglycation activity.

In the study, Maramaldi *et al.*²⁵ found that purified CA extract protected DNA from damages caused by UV lights by decreasing photo dimerized thymine up to 28% ($p < 0.05$). Expression of interleukin 1 α also lowers up to 26% ($p < 0.01$), supporting *C. asiatica* as an antiinflammatory agent. In this study, *C. asiatica* purified extract completely prevented physiological glycation and was capable of compensating action of the glycating agent. Result of the *in vitro* study was confirmed by the clinical result, where intervention with *C. asiatica* 0.5% cream in healthy individuals improved wrinkle depth and volume, skin elasticity, and skin texture significantly ($p < 0.05$).

The molecular dynamic (MD) simulation study explored the molecular docking of *C. asiatica* active compound as an inhibitor of AGEs and receptor AGEs (RAGEs). Based on MD simulation in this study, *C. asiatica* active compounds have been proven to interact with both AGEs and RAGE. AGEs bound to asiaticoside, madasiatic acid, and madecassic acid with significant binding energy. Nonetheless, Asn106, Asp324, Asp376, Tyr420, and Tyr500 of AGEs made a significant contribution to the complex of asiaticoside-AGE. In the madasiatic acid-

AGEs, significant contribution was made by Asn118 and Tyr500. Meanwhile, it was found that RAGE bound to asiaticoside, asiatic acid, and isothankunik acid with significant binding energy.³⁵

Study of *C. asiatica*'s benefits

Moertolo *et al.*³⁶ studied *C. asiatica* extract topical in atrophic scar post-acne vulgaris. This *in-vitro* study used fibroblast cell culture which was given CA extract concentration 0.6%, 0.8%, and 1.0%. Results showed *C. asiatica* significantly elevated fibroblast proliferation, depressed TNF- α , and metalloproteinase-1 (MMP-1) concentration, and also promoted collagen I and III. Furthermore, the study was followed by an *in vivo* experiment with *C. asiatica* 0.8% mask in 94 subjects. The *in vivo* experiment found that *C. asiatica* 0.8%. The mask promoted faster healing and prevented atrophic acne scar formation compared to control.

Centella asiatica was also studied for its antioxidant properties. In a 2015 study by Mohamed and Abdou,³⁷ mice with streptozotocin-induced DM treated with *C. asiatica* 250 mg/kg/day for 14 days showed an elated antioxidant capacity of the pancreatic cell and decreased MDA significantly compared to control. Another report found by Abdou and Mohamed,³⁸ consumption of *C. asiatica* with the dosage of 250mg/kg/day for 28 days improved superoxide dismutase (SOD), catalase (CAT), redacted glutathione (GSH), glutathione peroxidase (GPX), and lowered lipid peroxidase significantly in mice with streptozotocin-induced DM.

Topical use of *C. asiatica* extract is often associated with low bioavailability, poor fat solubility, and large molecule size, decreasing its absorption to skin and slowing skin distribution. Its efficacy *in vivo* is thus questioned. However, several studies had found that topical *C. asiatica* application still benefits the

skin despite its low bioavailability.³⁹ Maramaldi *et al.*²⁵ found that topical 1% *C. asiatica* application in human skin explant showed antiinflammation and antiglycation properties by decreasing IL-1 α and decreasing CML formation. This study was followed by a clinical experiment in healthy individuals which displayed that topical 0.5% *C. asiatica* improved wrinkles. Usage for 6 weeks improved wrinkle depth and volume, skin elasticity, and skin firmness significantly ($p < 0.05$).

Several studies look into the oral usage of *C. asiatica* extract. Anakunwithaya *et al.*⁴⁰ studied the bioavailability of standard extract *C. asiatica* (ECa 233) in rats, measuring the main constituents which were madecassoside (53.1%) and asiaticoside (32.3%). ECa 233 were absorbed rapidly, although not entirely, in the gastrointestinal tract 5-10 min after administration. Both madecassoside and asiaticoside were distributed extensively in the brain, stomach, and skin within 1 h and remained for at least 4 h. The oral bioavailability of madecassoside and asiaticoside were low. Madecassoside bioavailability was measured 0.19% for dose 50 mg/kg, 0.27% for 100 mg/kg, and 0.14% for 200 mg/kg. Meanwhile, asiaticoside bioavailability was measured 0.15% for dose 50 mg/kg, 0.26% for 100 mg/kg, and 0.16% for 200 mg/kg. Another study by Yuan *et al.*³⁹ found that the bioavailability of *C. asiatica* compound asiatic acid with a dose of 20 mg/kg was 16.25% in modeled rats.

***Centella asiatica* study in dry skin**

Past studies had found that topical *C. asiatica* was able to repair skin hydration by increasing aquaporin-3 (AQP-3) expression. Aquaporin-3 is a water channel that facilitates water movement from the dermis to epidermis. Nonetheless, topical *C. asiatica* has humectant ability which attracts moisture in the nearby environment

and deeper skin layer to repair dry skin conditions.⁴¹ Wijayadi *et al.*⁴¹ reported that *C. asiatica* extract ethanol in chitosan nanoparticle with a concentration of 3.125 mg/mL to 100 mg/mL was able to increase proliferation of fibroblast and keratinocyte, synthesis of collagen I and III, and expression of aquaporin-3 (AQP-3) in fibroblast and keratinocyte. This study was followed by a clinical experiment by Hasanah *et al.*⁵ which studied *C. asiatica* extract ethanol in chitosan nanoparticle 1% and *C. asiatica* ethanol extract 1% in cream preparation in elderly dry skin. After six weeks of follow-up, the study found that both *C. asiatica* ethanol in chitosan nanoparticle extract 1% and *C. asiatica* ethanol extract 1% improved dry skin, measured by specified symptom sum score (SRRC) and skin capacitance (SCap).

A comparative, three-arm RCT study analyzed the usage between of a combination of *C. asiatica* 2x1.100 mg oral and *C. asiatica* 1% topical (CAo + CA_t) and *C. asiatica* 1% topical (Plo + CA_t), and placebo (Plo + Plt) for treatment of dry skin in T2DM patients. The dry skin assessment (the measurement of SRRC and SCap) was performed on day 1, 15, and 29, while evaluation of CML, IL-1 α , and SOD activity was on day 1 and 29. The study found that after 29 days of treatment, the percentage of SRRC decrement in well-controlled blood glucose patients was greater in the CAo + CA_t group than the control group ($p = 0.04$). The SCap value on day 29, the CAo + CA_t group also was greater than the control group ($p = 0.01$). In the partially controlled blood glucose, the increment of SOD activity in the CAo + CA_t group was greater than the control group ($p = 0.01$). There was a medium-to-strong correlation between CML with SOD ($r = 0.58$, $p < 0.05$) and IL-1 α with SOD ($r = 0.70$, $p < 0.05$) in well-controlled blood glucose. In the study, systemic and topical adverse events were not significantly different between groups.⁴²

Dosage of *C. asiatica*

The recommended dosage for *C. asiatica* are mentioned below:⁴³ 1). Oral *C. asiatica* extract 60 mg 2-3 times/day, 2). *Centella asiatica* 1% cream daily. In *C. asiatica* studies, patients with chronic vein insufficiency were generally advised to consume *C. asiatica* supplement 2-3 times daily. Total saponin (asiatic acid, madecassic acid, asiaticoside, and madecassoside) were 30-60 mg per consumption with the total ranging from 60-180 mg daily. *Centella asiatica* also showed a potential benefit in enhancing cognitive function. Rats given 200-300 mg/kg *C. asiatica* dosage showed a significant increase in cognitive function. This study predicted that similar dosages would enhance cognitive function in humans; however, human study has not been conducted yet. Based on the calculation, 2100-3300 mg could be used in 68 kg, 2900-4400 mg could be used in 91 kg, 3600-5500 mg could be used in 113 kg. In another study, 500 mg of *C. asiatica* consumed two times daily was effective in treating anxiety in human. This study also concluded that 750 mg of 5% asiaticoside 5% was able to increase mood state.⁴⁴

A study observed asiaticoside plasma concentration in humans after consuming a total triterpenoid fraction 30-60 mg twice a day. The study found that a dosage of 30 mg increased asiaticoside plasma to 700 ± 110 ng/mL after single dose, and after 6 days the concentration in plasma was found to be 1.03 ± 0.05 µg/mL (T_{max} 4.1–4.5 h). Meanwhile, a 60 mg dosage increased plasma concentration to 1.36 ± 0.13 µg/mL and after 6 days the concentration peaked at 1.69 ± 0.07 µg/mL (T_{max} 4.2 h). Half time in humans varied in different dosage and duration, the half time when using single dose with 30 mg was 2.20 ± 0.30 h and 60 mg was 3.40 ± 0.68 h, then when consumed for 6 days 30 mg was 6.33 ± 1.82 h and 60 mg was 10.28 ± 1.8 h.⁴⁵

In Abdou and Mohammed³⁸ reported that 250 mg/kg/day *C. asiatica* in modeled rat ameliorated activity of SOD, CAT, GSH, and GPX, as well as lowered lipid peroxidase significantly in streptozotocin-induced DM model rat in 28 days. In another study, *C. asiatica* with dosage of 250 mg/kg/day enhanced antioxidant capacity in pancreatic cell and decreased MDA concentration compared to control in streptozotocin-induced DM model rat after 14 days.³⁷

Both dosages used in the study were 250 mg/kg/day in streptozotocin-induced DM modelled rat. This dosage in the rat model was then converted to human dose. Study by Reagan-Shaw *et al.*⁴⁶ calculated conversion to human dosage based on body surface area (BSA), estimated by 40.54 mg/kg.

In a study conducted by Legiawati *et al.*⁴² T2DM patients with dry skin were treated with a combination of *C. asiatica* 2x1.100 mg oral and *C. asiatica* 1% topical (CAo + Cat), *C. asiatica* 1% topical (Plo + Cat), and placebo (Plo + Plt). In the group treated with CAo + Cat with well-controlled blood glucose, there was a significant percentage of SRRC decrement and significant SCap improvement after 29 days of therapy. The study also found significant SOD activity increments in the partially controlled blood glucose group after 29 days of treatment with CAo + Cat.

Toxicity and safety

Test for acute toxicity in standardized *C. asiatica* extract (ECa 233) showed that a single dose of 10 g/kg was the highest dosage tolerable by rat models without acute toxicity effect, death, and pathological lesion. Therefore, LD₅₀ value to 10 g/kg indicated safety limitation for ECa 233 where the effective dose for memory enhancement was 10 to 30 mg/kg. In a test for subchronic toxicity, Wistar rats treated with ECa 233 with doses 10, 100, and 100 mg/kg/day for

90 days were not experiencing weight changes, food consumption, and health of model animals. There was a significant leucocyte count in the group treated with the highest dose, however it was not considered as leukocytosis. ECa 233 also did not induce any significant changes in blood chemistry or microscopic organ alteration.⁴⁷

Side effects commonly found in *C. asiatica* oral usage are intestinal problems, nausea, photosensitivity, pruritus, hypercholesterolemia, hypertension, hypertriglyceridemia, and sedation. In topical form, side effects of *C. asiatica* are allergic contact dermatitis. In spite of that, the frequency report of side effects was unavailable. There was no significant contraindication reported.⁴³

To this days, there was not any record of *C. asiatica* interaction with other drugs. Precaution must be taken while consuming *C. asiatica* with these drugs:

Sedative drug (central nervous system depressant)

Centella asiatica consumption could cause drowsiness. Combination of *C. asiatica* with these drugs will increase drowsiness. These drugs include clonazepam, lorazepam, phenobarbital.⁴³

Hepatotoxic drug

Several drug induced hepatotoxicity including: acetaminophen, amiodarone, carbamazepine, isoniazid, methotrexate, methylodopa, fluconazole, itraconazole, erythromycin, phenytoin, simvastatin.⁴³

Antidiabetic drug

Centella asiatica displays antidiabetic effect; thus, combination with other antidiabetic drugs is cautioned for hypoglycemia. Examples of commonly used

antidiabetics are acarbose, glimepiride, glikuidon, insulin, and metformin.⁴³

Jorge *et al.*⁴⁸ reported three cases of women age 61, 52, and 49 years old experiencing jaundice after consumption of *C. asiatica* for 30, 20, and 60 days. In this report dosage and formulation of *C. asiatica* were not mentioned. In the three patients, there was an increase of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and bilirubin. After *C. asiatica* was discontinued and ursodeoxycholic acid therapy was initiated at 10 mg/kg day, the three patients recovered.

Rahman *et al.*⁴⁹ studied the antioxidant effect of *C. asiatica* by measuring antioxidant capability of active compounds in *C. asiatica*. The active compounds were polyphenol, flavonoid total, β -karoten, tannin, and vitamin C. The study was conducted with three solvents, which are ethanol 100%, ethanol 50%, and water. The conclusion was that the reduction power of total 50% ethanol extract *C. asiatica* ($63.4 \pm 1.7 \mu\text{g AE/mL}$) was significantly higher than 100% extract ethanol CA ($40.4 \pm 0.7 \mu\text{g AE/mL}$) and extract water *C. asiatica* ($56.3 \pm 0.6 \mu\text{g AE/mL}$). The biological potential of CA extract was high and very hygroscopic thus the extract could survive in room temperature.⁵⁰

Three-arm study in T2DM patients with dry skin treatment was using *C. asiatica* 2x1.100 mg oral and *C. asiatica* 1% topical (CAo + CA_t), *C. asiatica* 1% topical (Plo + CA_t), and placebo (Plo + Pl_t). In the study, both oral and topical adverse events were addressed, with each subject experiencing more than one adverse event. The oral adverse events assessed in the study include gastrointestinal symptoms, sedation, increase in urination, abdominal pain, back pain, erectile dysfunction, hoarseness in voice, vertigo, palpitation, recurring urticaria, herpes zoster, Bell's palsy, and vaginal bleeding. The

oral adverse events were found to be indifferent between three groups. The topical adverse events complained by subjects were burning sensation, tenderness, and mild pruritus. However, the differences were insignificant among treatment groups. SGOT and SGPT were also measured on day 1 and 29 in all treatment groups. It was found that SGOT and SGPT value were not increased or differed significantly among the three groups.⁴²

CONCLUSION

Based on this review, dry skin in T2DM involves the pathological process of hyperglycemia and hyperinsulinemia. There are also several biostructural changes of the skin related to T2DM which induces dry skin condition. *Centella asiatica*, with its antioxidant, wound healing, antiinflammation, antiaging, anticancer, antidiabetic, neuroprotective properties is expected to improve dry skin condition of T2DM. Results of several studies conducted to observe *C. asiatica*'s benefits have been positive. Namely, clinical studies of *C. asiatica* have improved dry skin conditions in geriatric and T2DM patients. In addition, the toxicity, safety, and dosage.

ACKNOWLEDGEMENTS

We would like to thank you for all the support that have been given to the writer till the writing process of this study is conducted.

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