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Review article

Centella asiatica: A Potential Herb in the Arena of Dermatology

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Abstract: *Centella asiatica* a perennial, aromatic medicinal herb known as "miracle elixir of life" has been used as folk medicine and also scientifically oriented medicine. The medicinal herb, *Centella asiatica* (L.) Urban known as Gotu kola has been reported to exhibit a wide range of pharmacological activities. In particular, a remarkable body of scientific research exists on the therapeutic properties of preparations of *C. asiatica* or its triterpenes in the treatment of skin diseases. *Centella asiatica* has potent antioxidant and anti-inflammatory properties. The active compounds including penta-cyclic triterpenes, mainly Madecassoside, Asiaticoside, Asiatic and Madecassoside are effective in healing skin disorders such as repairing small wounds caused by injury or burns, heals atopic dermatitis, psoriasis, acne, eczema etc. TECA is purified standardized extract of *Centella asiatica* composed of Madecassic acid, Asiaticoside, and Asiatic acid.The mechanism involve wound treatment with TECA that collagen synthesis, fibroblast proliferation, management of keloids, regulating inflammatory cytokines and chemokines via TGF-β/Smad Signaling, NF-κ B Signaling. This madecassoside may significantly inhibit the production of IL-1β released by P. acnes stimulated THP-1 cells that might suppress P. acnes-induced inflammatory response. Also *Centella* play a pivotal role in cosmetology treating photo-ageing skin, cellulite and striae. The *C. asiatica* extract regulate the metabolism happening in the cells of the connective tissue, shows anti-inflammatory and draining activity and modulates microcirculation.

Keywords: Acne, Atopic Dermatitis, Burns, *Centella asiatica,* Madecassoside, Photo-ageing.

Introduction

India, a country having history of thousands of years, and rich legacy of science and arts. From the dawn of civilization, plants are indispensible to man. The three basic necessities of life, food, clothes and shelter besides maintenance of Indian culture, religious and spiritual purposes are provided to him by plant kingdom. The study of diseases and healing with medicinal plants is as old as mankind itself. The herbal medicine history is as old as human civilization. Learned persons of Vedic culture were quite aware regarding unimaginable obligation of plants for the very sustenance of life. May it be our regular skin care, hair care or fighting with common diseases such as cough, cold, asthma, diabetes etc to some serious neurological problems in every aspects nature cater its complete storehouse of remedies. Herbal medicine has elaborate uses reaching to the root cause of the disease and curing it without leaving any other serious side effects.

Pollution, a serious threat to mankind poses some major diseases one of which is dermatological disease. Dermatology is the branch of medicine that deals with the diagnosis and treatment of skin diseases. Skin diseases are the conditions that affect the skin causing rashes, itchiness, swelling, redness and some severe changes in skin. Skin disease can be

genetically or may be due to environmental factors and also lifestyle habits. Skin is the vital organ for covering our body, protecting from dehydration, keeping away bacteria, viruses and different reasons of infection, synthesize Vitamin D in response to exposure of sun. In one word skin is the main line of defense which acts as a barrier to any foreign objects. There are many herbal remedies and also herbal products available in market nowadays to keep our skin healthy and to keep away some major dermatological diseases. Medicinal plants are effective for the skin diseases mainly due to the activity of various active ingredients present in those plants.

One such plant is *Centella asiatica* also known as "Thankunipata" (vernacular name in Bengali). *Centella asiatica* is a small herbaceous annual plant belonging to Apiacea (Umbelliferae) synonyms includes *Hydrocotyle asiatica*. L.and *Trisanthus cochinchinesis* Lour. *Centella* is a very important medicinal herb, also gaining popularity in the West (Chevallier, 1996). Commonly known as either Indian pennywort jalbrahmi, has been effectively used as medicine in the Ayurvedic culture of India since thousands of years and enlisted in the historic 'Sushruta Samhita', an ancient Indian medical content (Chopra *et. al.*, 1986).

Distribution

Centella seems to have been originated in the wetland of China, India, Asia and Malaya. It is spread through the South Pacific and to Mauritius, Madagascar, East and South Africa, Turkey, etc (Kuntal Das. 2010).

Habitat

Centella grows along ditches and in low wet areas.

Botanical Classification of *Centella asiatica* : According to APG-4

Kingdom: Plantae
Clade: Tracheophytes
Clade: Eudicots
Clade: Asterids
Order: Apiales
Family: Apiaceae
Genus: *Centella*
Species: *C.asiatica*
Binomial Name *Centella asiatica* (L.) Urban

Botanical Description

It is a perennial herb creeping along the ground and rooting at leaf nodes. This is a prostate, sparingly hairy or nearly smooth herb. Stems slender, creeping stolon, which connect one plant with other, green in colour. Rootstock comprise of rhizome, creamish in color. Leaves are heart shaped, circular or reniform with regular lobed margin. The petioles are erect and long. The peduncles appear in three pairs, generally bearing 3 flowers without stalk. Flower dark pink in colour, ovate and overlapping. Fruit compressed sideways, reticulate with nine sub similar longitudinal ridges (Kuntal Das. 2010; Satake T *et al.*, 2007; Zheng CJ and Qin LP. 2007). [Fig. A, B, C]

Fig. A- Leaves; Fig. B- Stem; Fig. C- Flower
Source: Sakshi Singh, AsmitaGautam, Abhimanyu Sharma and Amla Batra.2010. *Centella asiatica* (l.): a plant with immense medicinal potential but threatened. Vol 4, Issue 2, Article 003.

Chemical Composition

Triterpenoids, one of the major active ingredients in *Centella* is responsible for its wide health-curing benefits.

Pharmacological Effects of *Centella asiatica* on Skin Diseases

Centella is used as culinary herb and as medicinal herb showing wide benefits for treating some major skin problems. Besides wound healing this miraculous herb is advised for treating several skin conditions like leprosy, varicose ulcers, lupus, eczema, psoriasis.

The roles of *Centella asiatica* in the field of dermatology is tabularized in Table 2.

Table 1. Active ingredients in *Centella asiatica*

Main Group	Constituents	Reference
Triterpenoids	Triterpenes, asiaticoside, centelloside, madecassoside, brahmoside, brahminoside (saponin glycosides), asiaticentoic acid, centellic acid, centoic acid, madecassic acid, terminolic acid and betulic acid.	(Barnes *et al.*, 2007; Jamil *et al.*, 2007)
Volatile and fatty oils	Fatty acids: linoleic acid, linolenic acid, lignocene, oleic acid, palmitic acid, stearic acid.	(Barnes *et al.*, 2007; Jamil *et al.*, 2007)
Alkaloid	Hydrocotylin ($C_{22}H_{33}NO_8$)	(Chopra *et al.*, 1956).
Phenols	Flavanoids: Kaempferol, castilliferol kaempferol-3-o-d-glucuronide, quercetin-3-o-d-glucuronide, ,quercetin, castillicetin, apigenin, rutin, luteolin, naringin. Phenylpropanoids: Rosmarinic acid, 1,5-di-o-caffeoyl quinicacid,chlorogenic acid, 3,4-di-o-caffeoyl quinic acid, 3,5-di-o-caffeoyl quinic acid, 4,5-di-ocaffeoyl quinic acid, isochlorogenic acid Tannin: Tannin, phlobatannin	(Bhandari *et al.*, 2007; Zheng and Qin, 2007; Chong NJ and Aziz, 2011) (Chong NJ and Aziz, 2011) (Chong NJ and Aziz, 2011)
Vitamins	Ascorbic acid, nicotinic acid, carotene	(Chong NJ and Aziz, 2011)
Mineral	Calcium, phosphorus, iron, potassium, magnesium, manganese, zinc, sodium, copper	(Chong NJ and Aziz, 2011)

Wound healing

Wound is disruption to the physical and functional tissue or in short injury to the skin caused by tear, cut or contusion. Wound healing is a complex biological process involving coagulation, inflammation, cytokine production, cell migration, proliferation and differentiation, angiogenesis, synthesis and remodeling of extracellular matrix (including collagen production and deposition). Type I and III collagen are the major components of the skin extracellular matrix. Both types play an important role in the wound healing process. As a result, proliferation of epithelial cells and wound contraction occur (Lu *et al.*, 2004a, 2004b; Liu *et al.*, 2008) Several studies by the researchers have revealed that different extracts of *Centella asiatica* play a major role in wound healing due to the presence of the vital triterpenoids components. Among the triterpene compounds Asiatic acid, asiaticosidemadecassic acid, and madecassoside are the chief components of *C. asiatica* which are responsible for wound healing. The terpenoids cause a remarkable increase in the percentage of collagen and cell layer fibronectin. The most advantageous effects are inducement of maturation of scar by the formation of type I collagen, reduction in the inflammatory response and myofibroblast production.

TECA (Titrated Extract of *Centella asiatica*) is purified standardised extract of *Centella asiatica* composed of Madecassic acid, Asiaticoside, and Asiatic acid Wound treatment with TECA increase total protein, collagen, and peptic hydroxyproline content. These contents induce cell migration from the peripheral tissues and activate some growth factors in the wound thereby resulting in rise of fibroblast proliferation

The triterpenoid components also able to stimulate glycosaminoglycan, especially hyaluronic acid synthesis (Maquart FX *et al.*, 1999). Asiaticoside stimulate angiogenesis causing increase in tension and elasticity of blood vessels (Shukla A *et al.*, 1999). Asiaticoside increase hydroxyproline content and enhance tensile strength, rise collagen content and better epithelisation of punch/puncture wounds in diabetes induced guinea pigs (Shukla A *et al.*, 1999). The mode of action of asiaticoside is stimulation of type I collagen synthesis by phosphorylation of both Smad 2 and Smad 3, also binding Smad 3 and Smad 4. Studies revealed that asiaticoside can

stimulate type I collagen by activation of tumour growth factor β(TGF-β) receptor I kinase – independent Smad pathway (Lee J *et al*., 2006).

Keloids are developed by the more proliferation and deposition of collagen, also known as fibro proliferative lesions. This occurs due to abnormal healing and causes collagen proliferation beyond the wound margins (Scott *et al*., 2021). Extract of *C. asiatica* has also been helpful for the management of keloids.

Transforming growth factor- β1 (TGF-β1) plays a role in this pathology, as it induces collagen formation, while plasminogen activator inhibitor 1 (PAI-1) prevents the action of plasminogen activators. These are responsible for the dissolution of clots, which seal blood vessels, protecting them and preventing blood loss. Therefore, the inhibition of both TGF-β1 and PAI-1 by Asiatic acid,one of the major constituents of *C. asiatica,* makes it a promising compound for successful management of keloids.

Burns

Burn is a dermal damage or injury to the tissue caused by heat, chemicals or radioactive radiation causing red spot, inflammation, splotchy skin, and blisters with severe pain. Burn results in release of multiple pro-inflammatory mediators, reactive nitrogen and oxygen species, causing a post-burn systemic inflammatory response. Growth factors and various cytokines activate keratinocytes and fibroblast soon after inflammatory response. These keratinocytes and fibroblast restore vascular perfusion and promote wound healing. Further Collagen and elastin then deposit to transform fibroblast to myofibroblasts. An intricate balance between contraction of myofibroblasts and re-epithelialisation determines the quality and pliability of the repaired wounds and ascertain the scar formation extent, which is characterized by fibrous malposition of collagen fibers (M. P. Rowan, *et al*., 2015). Asiaticoside and madecassoside, key ingredient of *Centella asiatica* contribute to its burn healing property. Topical treatment with asiaticoside and madecassoside not only induced collagen synthesis, proliferation, and cell growth but also stimulated burn wound healing in male ICR mice. CytolCentella®is a commercial cream formulated with a titrated extract of *C. asiatica*. Topical application of CytolCentella® remarkably stimulates burn wound contraction by enhancing collagen synthesis in male Wistar rats (S. Bardaa *et al*., 2016).

Topical application with Centiderm ointment prepared from *C. asiatica*ethanolic extract significantly improvise the objective (pigmentation, vascularity, height, pliability, and visual acuity scores) and subjective (irritation, dryness, and itching) symptoms in patients with second-degree burn wounds on their limbs. (A. Saeidinia *et al*., 2017).

TGF-β/Smad Signaling

Transforming growth factor-β (TGF-β) plays a pivotal role in producing the myofibroblast phenotype, which is responsible for massive collagen deposition and contraction of wounds (J. M. Carthy. 2018). Since the TGF-β-induced Smad-dependent pathway is crucial for the pathogenesis of all fibrotic diseases, different therapeutic strategies have been investigated to target the signalling pathway to attenuate aberrant skin scar formation (T. Zhang *et al*., 2020). Among the triterpenoid compounds of *C. asiatica*, the glycosides (madecassoside and asiaticoside) themselves, rather than their corresponding metabolites, asiatic acid and madecassic acid, are recognized as the main active constituents of *C. asiatica* herbs responsible for burn wound healing.

Atopic dermatitis

Atopic Dermatitis commonly referred as eczema is a common form of inflammatory skin disease that stimulate skin itching, redness and irritation, thickening and hardening of skin, lesions. Intense pruritus and cutaneous reactivity are the cardinal features of AD. It is not contagious and is a chronic condition that may last throughout life. The result of complex interactions among susceptible genes, the host's environment, problem in skin barrier function, and systemic and local immunologic response are the clinical phenotype that marks AD. The primary T-cell immunodeficiency diseases frequently have

high serum IgE levels, eosinophilia, and eczematoid skin bruise similar to atopic dermatitis. Thus the pathogenesis of Atopic dermatitis involve immunological basis, defects in cell-mediated immune responses, and changes related to barrier dysfunction (W. David Boothe *et al.*, 2017)

Th2 dysbalance with increased IgE levels and eosinophilia is widely accepted in the pathogenesis of atopic diseases. There is surge in the production of Th2 mediated cytokines, notably IL-4, IL-5, and IL-13, which can be observed in lesional and non-lesional skin during the acute phase of disease. There are series of interleukin which are implicated in different phases of this disease such as follows

In the initial phase of tissue inflammation and in up regulating the expression of adhesion molecules on endothelial cells IL-4 and IL-13 are implicated. IL-5 seems to increase the survival of eosinophils and this increase of the eosinophilia and eosinophilic cationic protein (ECP) are characteristic for a high disease activity of Atopic Dermatitis. In chronic AD skin lesions an increase of IFN-γ and IL-12, as well as IL-5 may be observed.

The Atopic Dermatitis skin lesions are regulated by the local tissue expression of pro inflammatory cytokines and chemokines. Cellular signaling including NF-κB pathway is activated due to the binding of Cytokines such as TNF-α and IL-1 from resident cells (keratinocytes, mast cells, and DCs) to receptors on vascular endothelium.

Underlying mechanism for the effect of *Centella* on Atopic dermatitis

NF-κB Signaling

The NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells) transcription factor family is a pleiotropic regulator of different cellular signaling pathways, providing a technique for the cells in response to a broad variety of stimuli linking to inflammation. Nuclear factor-kappa B (NF-κB) coordinate inflammatory responses, innate and adaptive immunity, and cellular differentiation, proliferation, and survival in almost all multicellular organisms (S. Mitchell *et al.*, 2016). The NF-κB system is tightly regulated, and misregulation of NF-κB has been implicated in a wide range of diseases ranging from cancer to inflammatory and immune disorders. As a consequence, the NF-κB regulatory components and its dynamics provide profuse promising therapeutic targets that are to be completely explored and translated into clinical use (JD Kearns and A Hoffmann. 2009).

Titrated extract of *C. asiatica* (TECA) treatment repressed NF-κB activity and eventually inhibit the expression of TNF-α, IL-6 and IL-1β in a phthalic anhydride (PA)-induced atopic dermatitis (AD) animal model" (J. H. Park, *et al.*, 2017). Another close report proves the therapeutic effect of *C. asiatica* on AD via NF-κB signaling. Topical treatment with *C. asiatica*phytosome inhibited the translocation of NF-êB into the nucleus and the release of TNF-α, IL-1β, and IgE, leading to the suppression of inflammatory cell infiltration (J. H. Park *et al.*, 2018).

Acne

Acne is a very common chronic skin disorder that happens generally when the hair follicles get clogged by oil, dead cells or bacteria. The pathogenesis of acne is regulated by sebum hyper-secretion in deformed follicles and this resulting skin condition favors the anaerobic growth of *Propionobacterium acne* which is the causative microorganism of acne. Hyper colonization of *P. acne* leads to generation of ROS and this ROS including singlet oxygen, superoxide anion, hydroxyl radical, hydrogen peroxide, lipid peroxide and nitric oxide (NO) play a vital role in inflammatory acne as well as in tissue injury.

Acne inflammation is the major threat to skin integrity for the adolescent people and harmful to skin homeostasis (Rocha MA, *et. al.,* 2018). Some other bacterial strains (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*) could also partly exacerbate acne inflammatory event, but are far less significant than P. acnes (Poomanee W. *et al.*, 2018).

Purified madecassoside is the main pentacyclic triterpene saponin from C. asiatica. This madecassoside may significantly inhibit the production of IL-1β released by P. acnes

Table 2. Role of *Centella asiatica* in the field of dermatology.

Extract/Constituents	Role in the field of Dermatology	Cited reference
	Wound healing	
TECA, asiatic acid, madecassic acid and asiaticoside.	Increase proline level, collagen synthesis.	Maquart *et al.*, 1990
Asiatic acid, madecassic acid, asiaticoside.	Increase Type I synthesis.	Bonté *et al.,* 1994
Asiatic acid, madecassic acid, asiaticoside.	Stimulate glycosaminoglycan, especially hyaluronic acid synthesis.	Maquart FX *et al.,* 1999
Asiaticoside	Stimulate angiogenesis causing increase in tension and elasticity of blood vessels.	Shukla A *et al.*, 1999
Asiaticoside	Increase hydroxyproline content, enhance tensile strength, rise collagen content and better epithelisation of punch/puncture wounds in diabetes induced guinea pigs.	Shukla A *et al.*, 1999
Asiaticoside	Keloid-derived fibroblasts/increase collagen synthesis, normalization of healing process	Tang *et al.*, 2011
	Burn healing	
Madecassoside	Burn wound, increase antioxidative activity, collagen synthesis, angiogenesis/ oral administration in mice.	Liu *et al.*, 2008
Asiaticoside	Burn wound/influence on the level of cytokines, increase angiogenesis, stimulation VEGF production, MCP-1, IL-1/topical application on the backs of mice	Kimura *et al.*, 2008S.
Cytol Centella® (commercial cream formulated with titrated extract of *C. asiatica*)	Topical application remarkably stimulates burn wound contraction by enhancing collagen synthesis in male Wistar rats.	Bardaa *et al.*, 2016A.
Centiderm ointment (prepared from *C. asiatica* ethanolic extract).	Topical application with significantly improvise the objective (pigmentation, vascularity, height, pliability, and visual acuity scores) and subjective (irritation, dryness, and itching) symptoms in patients with second-degree burn wounds on their limbs.	Saeidinia *et al.*, 2017
	Atopic dermatitis	
Titrated extract of *C. asiatica* (TECA)	Repressed NF-κB activity,inhibit the expression of TNF-β, IL-6 and IL-1αin a phthalic anhydride (PA)-induced atopic dermatitis (AD) animal model.	J.H. Park *et. al.,* 2017
	Acne	
Madecassoside	Significantly inhibit the production of IL-1α released by *Propionobacterium acne,* stimulate THP-1 cells that might suppress *P. acnes*-induced inflammatory response, decrease TLR2 expression.	Lawrence T. 2009

stimulated THP-1 cells that might suppress P. acnes-induced inflammatory response. Madecassoside decreased TLR2 expression and the inhibited activation of the NF-κ B signaling pathway. NF-κ B directly bound to the IL-1β gene promoter and activated its transcription (Lawrence T. 2009), so the inhibited translocation of NF-κ B might also account for the down-regulation of IL-1β mRNA expression. Hence madecassoside could suppress inflammation activities of P. acnes via a mechanism of diminished NF-κ B activation and TLR2-mediated signaling pathways, similar to a previous study on *Rosmarinus officinalis* extract (Tsai TH, *et al.*, 2013) (Fig. D).

Role of *Centella* in cosmetology

C. asiatica has also vividly excel its effectiveness in the field of cosmetology. It has been vividly used as a beneficial anti-photo aging agent, mainly because of enhancement of type I collagen, which decreases in skin with age. Madecassoside which is an inducer of collagen expression that activate the

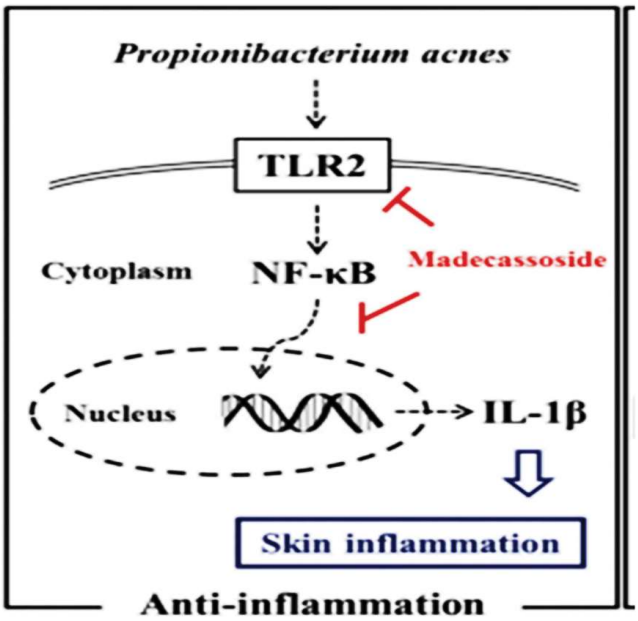

Fig. D -Underlying mechanism for the effect of *Centella* on *Propionobacterium acne.*

Source: Xueqing Shen et.al, 2019. Propionibacterium acnes related anti-inflammation and skin hydration activities of madecassoside, a pentacyclic triterpene saponin from *Centella asiatica*, Bioscience, Biotechnology, and Biochemistry 2019, VOL. 83, NO. 3:561–568.

SMAD signaling pathway is regarded as the cause for the beneficial effect of *C. asiatica* on improving the condition of skin. Vitamin C, an important component for photo aged skin that resulted from induction of collagen synthesis in fibroblasts and management of matrix metalloproteinase enzymes responsible for degeneration of collagen. Thus it follows that the mixture of vitamin C and madecassoside is an attractive combination of two active compounds characterized by different mechanisms of activity, which exert an additive or synergistic effect "causing the remodeling of the superficial dermis" (Haftek M *et al*., 2000).

Centella asiatica is a basic ingredient of cosmetics used in cellulite and striae. Cellulite, also called as liposclerosis, is a non-inflammatory change within the subcutaneous adipose tissue developed by deposition of fat cells or by increased division of the connective tissue, which result in constriction of small blood vessels. The result is a disorder of metabolism in the subcutaneous adipose tissue, resulting in "distended" fat cells in this tissue, particularly around hips, buttocks, abdomen, thighs and arms. Cellulite is an illness that attack many people, most often women, especially obese and leading sedentary lifestyle, but may even be encountered in children.

Preparations made from plant origin which is better to fight against cellulite that influence the adipose tissue, connective tissue and ameliorate microcirculation, can be used topically, and transdermally.

The *C. asiatica* extract regulate the metabolism happening in the cells of the connective tissue, shows anti-inflammatory and draining activity and modulates microcirculation. The triterpenes of *C. asiatica* increase the metabolism of lysine and proline, the amino acids that build the collagen molecule. Moreover these compounds enhance the synthesis of tropocollagen, and mucopolysaccharide in the connective tissues. Thus *C. asiatica* have impact on improving nutrition of tissues and connective vascular stimulation (Goldman MP *et al*., 2006).

Conclusion

Centella asiatica commonly known as Thankuni is beneficial for different dermatological diseases. It has been proven scientifically that it effectively treat wounds, burns, acne, atopic dermatitis, psoriasis etc. The active constituents of *C.asiatica* including pentacyclic triterpenes, mainly madecassoside, asiaticoside, asiatic and madecassic acid are regarded as main cause for this beneficial role of *Centella asiatica*. The probable mechanism of action is increase in collagen synthesis, reduction in inflammatory response and myofibroblast production, increasing fibronectin content, activated SMAD pathway and successful management of keloids.

Some studies also suggest that *C.asiatica* is used as common ingredient in cosmetic industry. It acts as anti-photo ageing agent, and treats cellulite and striae.

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