



Exploring the Role of *Mandukparni* (*Centella Asiatica* (L.) Urban) As Antifungal Agent Via Phytosomes Technology as a Novel Approach in Drug Discovery in Targeted Treatment of Fungal Infection in Type II Diabetes Mellitus

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ABSTRACT:

Type II Diabetes Mellitus (DM) is one of the diseases in metabolic triad syndrome categorized in Lifestyle Disorders. Patients suffering from Type II Diabetes Mellitus often manifest themselves with fungal infection of skin, which is a recurrent infection requiring extensive treatment and hence, requires newer drug discoveries to curb the same. In the same line, Charak Samhita explains, causes of diseases due to metabolic derangement which includes Type II DM and advocates predominant use of herbs possessing bitter taste. With this background, the herb Mandukparni (*Centella asiatica* (L.) Urban) growing in marshy habitat and is known to harbor endophytic fungus on itself through symbiosis leads to production of secondary metabolites by establishing biochemical communication; Primarily known for its cognitive effect, but this herbal drug remains unexplored in its action as an antifungal agent in patients of fungal infection in Type II Diabetes Mellitus. To understand this concept, the exact mechanism of perception of Mandukparni, its bitter taste on skin requires a detailed enquiry. Moreover, the action of *Centella* via Phytosomes technology in curbing the fungal infection could be possible way for new drug discovery to treat such patients. This review is a comprehensive learning of probable mode of action of Mandukparni (*Centella asiatica* (L.) Urban) growing the endophytic fungus leading to generation of secondary metabolites as antifungal agents and its application via phytosome technology in exploring as a new drug discovery in treatment of Fungal infection in Type II DM.

Introduction

Lifestyle Disorders are noncommunicable diseases which include ailments caused due to unhealthy lifestyle leading to major diseases of metabolic syndrome causing medical conditions like Obesity, Hypertension, Hypercholesterolemia / deranged cholesterol levels and Type II Diabetes Mellitus [1]. Primarily unhealthy sedentary lifestyle contributes to such ailments which not only add to morbidity but also early mortality as well.

Out of these medical conditions, as per the data published in 2023 by Indian Council of Medical Research – India Diabetes (ICMR INDIAB), the prevalence of diabetes is 10.1 crores [2]. Diabetes is characterized by major macro and micro vascular changes leading to nephropathy, retinopathy, neuropathy [3]. But apart from these long-term complications, patients suffering from diabetes type II typically present in out-patient department as patients of recurrent fungal infection. The burden of cutaneous fungal infection is vast among the Type II Diabetic



patient [4]. Ayurveda mentions these diseases due to sedentary lifestyle, the causes of which are attributed to excessive intake of diet predominantly which is oily, excessive intake of sweet taste, diet not easy to digest. Moreover, as regards sedentary lifestyle Ayurveda mentions the person who has aversion for physical activity and the person who sleeps during the day time also who spend maximum time sitting), such patients leads to lifestyle disorders [5]. Acharya Charak discusses these diseases in depth which includes Type II DM) with associated dermatological conditions and Obesity etc. [6]. It is pertinent to note that, cutaneous manifestation is commonly mentioned in Ayurveda under lifestyle disorders and hence, it is important to explore varied treatment options for the same. Type II DM characterized by polyuria, [7] it is mandatory that this excessive moistness in the body called as *kleda* in Ayurveda to be treated with herbal drug with dry attributes. Among the six taste mentioned in Ayurveda, bitter taste predominately is used as a part of treatment protocol in Type II Diabetes which has action of drying up excess moistness within the body [8]. On this background, in view of novel drug discovery which has to be bitter tasting and will work on dermatological conditions especially on cutaneous fungal manifestation in Type II Diabetes, *Mandukparni* (*Centella asiatica* (L.) Urban) has been comprehensively studied. Growing in marshy habitat and known to harbor endophytic fungus on itself without causing symptoms of disease in host plant of *Centella*, consequently leading to production of secondary metabolites; Primarily known for its cognitive effect, but this herbal drug remains unexplored in its action as an antifungal agent in patients of fungal infection in Type II Diabetes Mellitus. Hence, this research article discusses the exact mechanism of perception of *Centella*, its bitter taste on skin through G-Protein coupled receptors (GPCR) in Type II DM. Moreover, it also further discusses proposed mode of action of the drug and the novelty of drug usage in treatment protocols via *centella* phytosomes in treatment of Cutaneous Fungal infection in Type II DM.

Methodology

In this review article, Ayurvedic contemporary texts and websites have been documented precisely which includes literature review of lifestyle disorders due to over nourishment, bitter taste – in Ayurveda and in

Modern light of Extraoral taste receptors, Concept of G Protein coupled receptors (GPCR) on Type II DM and perception of Bitter taste through GPCR, the review of herb *Centella*, its attributes of pharmacodynamics, literature on endophytic fungus growing on *Centella*, and role of this herb as *centella* phytosomes as proposed treatment protocol of fungal infection in Type II DM has been enumerated in detail.

Concept of Lifestyle Disorders – Type II DM in Ayurveda

In Ayurveda, the causative factors for manifestation of Type II Diabetes Mellitus due to sedentary lifestyle which forms the background for Obesity is well documented. While discussing the treatment protocols of dermatological manifestations in Lifestyle Disorders, it has been recommended that local application of powdered formulation of medicinal herbs like *Musta* (*Cyperus rotundus*), *Aragvadha* (*Cassia fistula* Linn.), *Patla* (*Stereospermum suaveolens*), *Triphala* (*Amalaki-Phyllanthus emblica* L., *Bibhitaki* – *Terminalia bellirica* (Gaertn.) Roxb., *Haritaki* (*Terminalia chebula* Retz.), *Neem* (*Azadirachta indica* A. Juss.), *Haridra* (*Curcuma longa* L.), *Daruharidra* (*Berberis aristata* DC), *Kutaja* (*Holarrhena antidysenterica* Linn.) etc. are advised as therapeutic powder massage, for bathing purpose which aids in curing the excessive moistness underneath the skin [9]. It is noteworthy that the drugs used in the treatment of skin manifestation in Type II DM are primarily bitter in tastes which possess attributes that causes dryness on application on skin.

Concept of Bitter Taste in Ayurveda and in Modern light of Extraoral Receptors

Concept of Taste is unique concept proposed by Ayurveda. Rasa is defined as direct and immediate action of a drug when it comes in contact with the taste receptors. There are total 6 tastes mentioned in Ayurveda viz., sweet, sour, salt, pungent, bitter and astringent [10]. Out of these excessive intake of sweet taste has been documented to cause over nourishment leading to obesity and manifestation of Type II DM and associated other diseases / symptoms due to aggravated *Kapha dosha* – (body humor as per Ayurveda) [11]. The treatment of skin manifestation due to aggravation of *Kapha* and *Pitta* (body humors mentioned in Ayurveda) underneath the skin it has been proposed as usage of



herbal medicines of predominantly bitter taste [12]. Further, while documenting the characteristic features of bitter taste it has been mentioned that it is therapeutic neutralization from any poison and therapeutic procedure of disinfection and disinfestation and causes drying of watery waste [13].

In view of modern light, it has been recently understood that the taste receptors are not bounded or confined to only oral cavity, but uniformly distributed in the entire body. It is suggested that these extra oral taste receptors are a part of large diffuse chemosensory system (DCS), which play a major role in maintaining the physiological states of the human body [14]. DCS is an anatomical structure made up of chemosensory cells either solitary or in the form of clusters. In precise, these DCS cells may express molecules of the chemo-receptorial cascade which are G-protein gustducin, which is known to play a major role in the expression and physiological actions of bitter taste in the body [15].

Concept of Concept of G Protein coupled receptors (GPCR) on Type II DM, Skin and Bitter Taste

G-Protein Coupled Receptors (G-PCRs) are group of protein receptors on the bi-lipid cell membrane. These receptors are responsible for functions of metabolism, immune response and brain function. G-PCRs make its use by attaching to naturally occurring substances called as ligands which are present outside the cell. A ligand is a substance that forms a complex with a biomolecule to serve a biological purpose [16]. The binding of ligands with their respective receptor typically results in a change of conformation of the target protein. After binding of ligands with GPCRs, there is change in shape of the receptors leading to transmission of signaling within the cell. These same receptors, GPCRs in the gut-brain-pancreatic axis are important receptors in the postprandial control of metabolism. Hence, GPCRs are new therapeutic targets for treatment of Type II DM [17].

GPCRs are largest family of plasma membrane protein which exerts its action also on skin. Previous researches pertaining to the action of GPCRs on skin suggests that these ligands regulate melanocyte homeostasis, including pigmentation [18]. Also, dysregulation of GPCR signaling in the cell is attributes to various skin lesions occurring in numerous skin inflammatory

diseases [19]. There is limited research on the role of GPCR in cutaneous fungal infection.

The TAS2R proteins function as bitter taste receptors [20]. There are extensive studies on perception of bitter taste on its effects on human body especially on metabolic deranged diseases like Type II DM [21]. The perception of Rasa via sensory organ of skin is the concept proposed by Ayurveda and hence, this avenue of research forms a key player to comprehend the role of GPCRs as target receptors of therapeutic interest which govern the Type II DM, skin inflammatory response and also acts as receptors for Bitter taste ligands on to the skin.

Role of Bitter Taste Phytochemicals on Skin

Bitter phytochemicals are produced by plants and the same are used as dietary and therapeutic potentials in humans. It is interesting to understand that as humans have aversion for this taste, but plants produce bitter phytochemicals primarily as a part of defense mechanism for them, so that herbivores won't eat them and thus, their survival is taken care of. The bitter tasting phytochemicals in plants include phenols, terpenoids, alkaloids, flavonoids, glucosinolates and isothiocyanates [22]. Researches on bitter phytochemicals on skin, presence of TAS2Rs in the skin (GPCRs responsible for perception of Bitter taste) highlights their potential as drug targets for addressing skin aging, wound healing, inflammatory skin conditions, and also skin carcinogenesis [23]. Complete elucidation of GPCRs - TAS2R signaling pathway in the skin is still awaited and hence, the role of Bitter taste on skin (as sensory organ) forms a module for research in deciding the treatment protocols in fungal infection.

Review of Mandukparni (*Centella asiatica* (L.)Urban)

Mandukparni (*Centella asiatica* (L.) Urban) belonging to family-Apiaceae (Umbelliferae). It is a prostrate, faintly aromatic, stoloniferous perennial herb, upto 2 m long as cited in Figure 1.



Figure 1 Morphology of Mandukparni (*Centella asiatica*(L.)Urban)



Figure 2: Growth of Endophytic fungus on leaf of Madukparni (*Centella asiatica*(L.)Urban)

The herb is bitter in taste, light – easy to digest in property, and cold in potency with post digestive taste as Sweet [24] The phytochemicals of this herb are major constituents are saponin (medacoside, asiaticoside, medacassoside, asiatic acid, a new triterpenic acid) [25]. The whole plant is used for its therapeutic utility in Ayurveda clinical practice. This herb is primarily known for its cognitive effect – increases cognition/ promotes intelligence mentioned as *Medhya rasayana* known for enhancing the complexion) [26]. Apart from that Nighantus (textbook of glossary of Ayurveda herbs) states that it is also recommended in dermatological conditions and Type II DM. [27]

Endophytic Fungus growing on Mandukparni (*Centella asiatica* (L.) Urban)

Endophytic fungi (EF) are a group of host-associated fungal clusters that inhabit the intercellular or intracellular spaces of host tissues, providing beneficial effects to their hosts. These fungal colonies infect the host plant without making it diseased. Moreover, once the host plant gets affected by this endophytic fungi, with the process of symbiosis it helps in preparation of secondary metabolites in plants via complex gene expression regulation mechanisms in the symbiotic continuum [28] as cited in Figure 2.

Hence, these are beneficial to the host plant which helps to increase the secondary metabolites in plants. As stated, *Centella* herb grows in marshy land and requires lot of water for sustaining itself. It is seen that this herb gets affected by Endophytic fungi due to excessive accumulation of water.

Previous researches on the growth of endophytic fungi on *Centella* states that, the common endophytes are the non-sporulating species followed by *Colletotrichum*, *Guignardia*, *Glomerella*, an unidentified ascomycete, the non-sporulating species 2 and *Phialophora* sp.[29]. Researches on endophytic fungi on *Centella* are suggestive of 13 endophytic fungi being isolated from the leaves of the plant, out of which one of the isolates produced asiaticoside. This asiaticoside producing isolate was identified as *Colletotrichum gloeosporioides* by the process of internal transcribed spacer-based rDNA sequencing [30]. Thus, the secondary metabolites asiaticoside produced by *Centella* play an important role in mediating biochemical communications between the host plant and endophytic fungi. These endophytic fungi thus, help in altering the genetic makeup of the plant, thereby, enhancing its therapeutic potential. As per previous researches asiaticoside is known for its therapeutic potentials suggest its activity as wound healing, venous insufficiency, anxiolytic properties, cognitive and antioxidant properties [31]. Further, in vitro studies of ethanolic extracts of *Centella* suggests antifungal activity along with other anti-microbial activity [32]. Hence, it can be summarized by these regulation mechanisms and production of secondary metabolites of asiaticoside have coevolved with the



initiation of Endophytic Fungi of *Colletotrichum* and – host plant (*Centella*) symbiosis.

Centella Phytosomes as novel drug in targeted therapy of Fungal Infection in Type II Diabetes Mellitus

Phytosomes are known as complex of phospholipids and natural active phytochemicals, bound in their structures, obtained by the reaction between phosphatidylcholine (or any hydrophilic polar head groups) and plant extracts in an aprotic solvent (solvents in which no hydrogen bonding takes place) [33]. These have emerged as novel pharmaceutical formulations for drug delivery system of natural compounds/ extracts [34]. These phytosomes have paved their way as an emerging nanotechnology pharmaceutical formulations for the topical delivery of bioactive phytochemicals [35]. Researches on *Centella* phytosomes are suggestive of having potent anti-inflammatory and antioxidant activity. On mouse model *centella* phytosomes are known for its anti dermatitic effect [36]. The compounds, asiaticoside exert therapeutic effects on dermatological diseases via NF- κ B, in in vitro and in vivo studies [37]

Discussion

With the present fundamental review study, it is evident that, for the treatment of Type II DM, which is included in triad of metabolic syndrome, bitter taste forms the integral part of treatment protocol. Excess amount of moistness in such patients in the skin forms a fertile ground for recurrent fungal infection. This fungal infection has limited treatment protocols which demands for discovery of novel drug therapies. By comprehending the mechanism of G Protein coupled receptors (GPCRs) on Type II DM, Skin and the properties of bitter taste is anti-toxic– neutralization of poison caused due to metabolic toxins, anti-fungal agent and aiding dryness by absorbing excess watery waste beneath the skin thereby, not facilitating the growth of fungus, followed by role of bitter phytochemicals on skin gives a detailed workup of how topical application of herbs with bitter taste can exert its therapeutic effect on skin which is also a sensory organ in medical conditions of fungal infection in Type II DM patients. With this background of GPCRs being major receptor mediating metabolism in Type II DM, bitter taste and the effect of role of bitter phytochemicals on skin allows one to search for herbal drugs for

combating fungal infection in diabetic patients. Review of *Centella* suggests that this herb is bitter tasting, it is a prostrate growing in marshy land, which itself naturally facilitates growth of fungus on it. Researchers suggest that out of 13 endophytic fungi isolated from *Centella*, the growth of endophytic fungus of *Colletotrichum* on *Centella* allows the biochemical communication. Without affecting the plant (no disease manifestation to the host plant), this endophytic fungus helps in enhancing the production of secondary metabolites of asiaticoside responsible for its dermatological effects. Previous in vitro studies of ethanolic extracts of *Centella* have shown promising results as a potent antifungal infection. These potentials of *Centella* for the purpose of novel emerging pharmaceutical formulation for topical drug delivery of bioactive molecule are explored via *Centella* phytosomes. These complexes allows natural bioactive phytochemicals of centella, asiaticoside is suggestive of anti-dermatitis effect in vivo mouse model. Further, *centella* phytosomes as antifungal agents on topical application requires further validation and studies via in vivo models followed by clinical trials.

Conclusion

Among the Non communicable diseases, due to metabolic derangement, Type II DM is an alarming disease; apart from that the burden of cutaneous fungal infection in patient with Type II DM is major. This condition is related to diseases caused due to over-nourishment as per Ayurvedic classical texts which also narrates cutaneous manifestation of skin. In search of novel drug discovery, to curb this medical condition, the present review gives insightful understanding of use of *Mandukparni* (*Centella asiatica* (L.) Urban) as *Centella* Phytosomes, in local application. The herb *Centella* being bitter, the mode of action of bitter taste as extra oral taste receptors via G protein couple receptors has been elucidated in this current article. Moreover, this article emphasizes the use of *Centella* after manifestation of endophytic fungus *Colletotrichum gloeosporioides* via symbiosis without affecting the host herb, rather helps production of secondary metabolites of asiaticoside responsible for dermatological effects. Further researches on use of *Centella* phytosomes which has been prepared after infestation of endophytic fungus *Colletotrichum gloeosporioides* may validate the present concept. In a nutshell, this review article opens up the



avenue of further research as role of *Mandukaparni* (*Centella asiatica* (L.)Urban) as antifungal agent via Phytosomes technology in targeted treatment of Fungal Infection in Type II Diabetes Mellitus.

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