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Perspective, Opinion, Commentary

Berberine from a Dermatologic Perspective

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Berberine is an isoquinoline alkaloid known for its wide range of antioxidant and pharmacological properties with use dating back over 2200 years. Though its role in dermatology is only beginning to be elucidated, berberine has shown potential in addressing a variety of skin conditions from S. aureus-exacerbated eczema to vitiligo, and now topical steroid withdrawal (TSW), with a comparatively low adverse event profile. The multifaceted anti-inflammatory, antioxidant, and antimicrobial properties of berberine render it a therapeutic agent with diverse benefits, prompting continued exploration of its potential role in dermatologic care.

INTRODUCTION

Berberine is an isoquinoline alkaloid known for its wide range of antioxidant and pharmacological properties. A bioactive phytochemical, it is primarily sourced from the Chinese herb *Coptis chinesis* and isolated from several medicinal plants including *Hydrastis canadensis*, *Berberis aristata*, *Coptis japonica*, *Phellondendron amurense*, *Phellondendron chinense Schneid*, and *Berberis vulgaris.*[1] The use of berberine, dating back over 2200 years, has been traditionally employed in Ayurvedic and Chinese medicine to treat various illnesses. According to *Shen-nong's Herbal Classic*, *C. chinesis* was used to prevent and alleviate digestive system symptoms such as abdominal distention, fullness, vomiting, acid regurgitation, diarrhea, and jaundice.[2] It was additionally employed to treat fever, vertigo, palpitations, hematemesis, epistaxis, conjunctival congestion, odontalgia, and cutaneous abscesses.[3]

Modern discoveries have identified berberine as a major component of *C. chinesis*. Its functions include possible anti-inflammatory, anti-infective, anti-tumor, antiarrhythmic effects as well as multi-organ protective capacities. Berberine may exhibit antimicrobial properties, targeting gastroenteritis and diarrhea by counteracting toxins and bacteria such as *Helicobacter pylori*. It may also simultaneously safeguard the intestinal epithelial barrier.[3] From a metabolic perspective, berberine may play a role in treating diabetes and dyslipidemia by modulating glucose and lipid metabolism, enhancing energy expenditure, mitigating obesity, and managing nonalcoholic fatty liver disease. Berberine also may provide benefits to cardiovascular health by improving hemodynamics, suppressing ischemic arrhythmias, reducing atherosclerosis progression, and lowering hypertension. The possibility of its neuroprotective effects are equally compelling with antioxidative, antiapoptotic, and anti-ischemic actions.[1] Moreover, berberine has been shown to potentially protect against polycystic ovarian syndrome and Alzheimer's disease.[4,5] Pharmacokinetic studies have demonstrated that berberine undergoes extensive metabolism following oral administration, with numerous active metabolites such as columbine, berberrubine, and demethyleneberberine. These metabolites alike contribute to berberine's pharmacological effects and exhibit a similar possibility of therapeutic benefits.[6]

Recently, a growing body of evidence suggests that berberine may possess anticancer effects, inhibiting proliferation of and enhancing cytotoxicity of cancer cells. In vitro studies on cancer cell lines are beginning to elucidate berberine's mechanism of action through various pathways including COX, NF-κB, STAT3, telomerase, and DNA binding, among others. These actions may result in cell cycle arrest, apoptosis, and regulated inflammation, highlighting the potential for berberine to pave the way for alternative cancer therapies.[5] With several recent discoveries demonstrating its therapeutic efficacy, berberine has been garnering recognition as a promising multi-modal, systemic therapeutic agent.

DERMATOLOGIC IMPLICATIONS

Berberine shows significant potential in therapeutic dermatology, particularly in the management of atopic dermatitis (AD). AD, also known as eczema, is a chronic inflammatory condition marked by recurrent, intensely pruritic lesions, often linked to a compromised skin barrier and immune dysregulation. Affecting millions worldwide with a lifetime risk of impacting 1 in every 10 individuals, AD remains a challenging and prominent issue in dermatology, necessitating early intervention and patient-centered modalities.[7,8]

Topical corticosteroids (TCS) are first line in management of atopic dermatitis (AD), as well as other inflammatory dermatological conditions.[9] Their use, however, remains constrained by factors such as duration, application location, and extent. In recent decades, there has been an increase in reports of severe systemic adverse reactions resulting from prolonged use and discontinuation of TCS, commonly known as Topical Steroid Withdrawal syndrome

(TSW).[10] Numerous cases have begun to define the characteristics of TSW based on its unique clinical features, distinguishing it from AD, contact dermatitis, and other dermatoses.[11] A recent analysis and pilot study by Shobnam et al suggests that the pathology of TSW may be linked to an overactivation of complex I, resulting in increased NAD+ oxidation either through increased expression of complex I or enhanced availability of NADH via tryptophan metabolism. Their findings show that berberine, a known complex I inhibitor similar to metformin, effectively improves cell culture outcomes in vitro, inhibiting oxygen consumption rates at concentrations as low as 0.6 μM. In a small, open-label pilot they conducted, 9 patients opted to take oral berberine from 500 mg-1500 mg daily. The authors specifically mentioned several brands they found had sufficient quality and were recommended (ie, Natural Factors, WellBetX, and Solaray) and they reported improvement in TSW symptoms in patients taking the oral berberine supplements.[12] This pioneering study positions berberine as a prospective candidate for TSW therapy.

In addition to TCS, conventional therapies such as other topical anti-inflammatories, systemic immunosuppressants, and biologic agents have demonstrated substantial efficacy in reducing the burden of AD. However, these therapies come with adverse effects such as increased risk of infections, malignancy, and other complications, as well as high costs. These challenges underscore the need for a more diverse range of therapeutic options.[13] Specifically, the increasing recognition of the role of *S. aureus* in driving AD emphasizes the need for more treatment options, with berberine showing promise as a potential solution.

A recent study by Maskey et al, presented at the 2024 American Society for Microbiology Microbe, explores the possibility of berberine as a candidate for managing eczema exacerbated by *S. aureus*.[14] This study investigated berberine's effect on the inflammatory response induced by *Staphylococcus aureus* isolated from eczema patients. After whole genome sequencing of these *S. aureus* strains to identify resistance genes and toxin-encoding genes, murine macrophage and human monocyte cell lines were treated with various concentrations of berberine and stimulated with heat-killed *S. aureus* strains. Findings demonstrated berberine's capacity to inhibit *S. aureus* colonization and mitigate eczema symptoms through its anti-inflammatory effects and inhibition of mast cell degranulation, highlighting its potential as a safe and effective therapeutic agent in atopic dermatitis progression. On further investigation, berberine was found to downregulate genes linked to inflammatory pathways and target key modulators in the PI3K/AKT pathways.[15] Other studies have also illustrated berberine's capacity to mitigate *S. aureus*-induced inflammation by inhibiting the release of TNF-α.[16]

Despite berberine's poor membrane permeability, numerous topical formulations have successfully implemented effective workarounds. Eczema mouse models demonstrate the effectiveness of a liposomes-in-gel berberine formulation for alleviating symptoms of pruritus, comparable to a dexamethasone control.[17] Several studies examining the efficacy of topical berberine formulations in management of psoriasis also show hopeful results. Topical application of berberine hydrochloride alleviated skin inflammation in imiquimod-induced psoriasis by suppressing the JAK1/STAT1 signaling pathway in mouse models.[18] The development of hydrogels incorporating berberine hydrochloride and a permeation enhancer is also currently underway.[19] Additionally, hyalurosomes used as a nanogel vehicle for berberine delivery present a feasible treatment modality for vitiligo, demonstrating favorable physicochemical properties and significant enhancement of biochemical markers in both in vitro and in vivo studies.[20]

There is limited evidence regarding the efficacy of oral berberine in treating skin diseases and related manifestations. A study in atopy-like dermatitis in mice demonstrated that oral administrations of berberine reduced skin symptoms, itching, and inflammatory cell infiltration by inhibiting eotaxin, macrophage migration inhibitory factor (MIF), IL-4, and related cytokine expressions.[21] Berberine additionally suppressed cytokine production by downregulating genes (EIF3F and MALT1) in mast cells. These findings suggest that berberine improves AD-like symptoms through the inhibition of pro-inflammatory cytokine expression and the related inflammatory cell recruitment. Further research is needed to determine the efficacy and safety of oral berberine for dermatological conditions.

Despite extensive preclinical research on berberine, its adverse effects remain poorly understood. Route of administration is a critical factor influencing berberine toxicity, with studies indicating that its acute toxicity is related to the administration method. Studies in mice have demonstrated median lethal doses for intravenous and intraperitoneal injections, while no lethal dose was identified for oral administration.[22] No serious adverse events have been reported for orally administered berberine, which has been deemed safe in the majority of human subjects studied, both in the short-term and over extended periods.[6] There has, however, been a report of transient gastrointestinal adverse effects following the high-dose administration of berberine (0.5 g, three times daily, over a three-month trial) in the treatment of type-2 diabetes mellitus patients.[23]

Other studies have identified a risk of kernicterus in infants, attributed to berberine's potential displacement of bilirubin from albumin, necessitating caution in its use among pregnant and breastfeeding women.[24] In addition, several drug interactions involving berberine and clinically significant medications have been documented, particularly in drugs metabolized by the liver.[25] Notable examples include the potential toxicity of warfarin, antagonism of L-DOPA, and enhanced efficacy of chemotherapies and fluconazole.[26] The low oral bioavailability of berberine warrants optimization of drug delivery systems alongside management of its toxicity. Existing clinical evidence regarding the adverse effects of berberine and its metabolites remains inadequate and warrants further clinical research.

Current research on berberine's application in skin disorders primarily focuses on its isolated form rather than its metabolites or whole-herb extracts. With a lack of studies comparing the efficacy of berberine's individual metabolites, whole-herb extracts, or different plant sources in

treating skin disorders, there is no established data on whether specific components or proportions are more effective for managing various skin conditions. As with all botanical treatments, it is important to acknowledge the variability in the composition and efficacy of active components, metabolite profiles, and that the herb's origin may significantly influence its treatment potential.

CONCLUSION

Berberine has distinguished itself as a viable alternative or adjunct for treating numerous common diseases, including diabetes, cancer, and obesity. Though its role in dermatology is only beginning to be elucidated, berberine already demonstrates great potential in addressing a variety of skin conditions from *S. aureus*-exacerbated eczema to vitiligo, with a comparatively lower adverse event profile thus far. The multifaceted anti-inflammatory, antioxidant, and antimicrobial properties of berberine render it a therapeutic agent with diverse benefits, prompting continued exploration of its potential role.

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