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Perspective, Opinion, Commentary

Theoretical Complementary and Alternative Therapies for Papular Urticaria: A Review of Potential Treatments based on Shared Pathophysiology

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Papular urticaria (PU) is a papulovesicular hypersensitivity reaction to arthropod bites, which most commonly affects children. The management of PU has traditionally been guided by treatment of itch and inflammation with medications such as oral antihistamines and topical corticosteroids along with removal of the offending agent. With the increased interest in the field of complementary and alternative medicine (CAM) among physicians and patients alike, we are led to investigate the theoretical role of turmeric, garlic, zinc, balneotherapy, quercetin, and rhododendron tormentosum (ledum palustre) in the treatment of PU, as they have been used in other inflammatory skin conditions with a similar immunological profile. Patients with PU predominantly respond to insect bites with increased CD4+ T-helper (Th)-2 cytokine production compared to healthy controls. However, the T-helper 1(Th1)/Th2 balance is nuanced in PU, with the delayed-type hypersensitivity stage and immediate hypersensitivity stage of the pathogenesis having propensities for a Th1 profile and Th2 profile, respectively. This finding is the highlight of this review, as most CAM agents examined influence the Th1/Th2 profile at varying doses and routes of administration. Although the anti-inflammatory role of these agents has been demonstrated in various systemic and cutaneous conditions, there is a paucity of well-designed, robust studies in the literature to formally declare efficacy in the treatment of PU. As with any traditional treatment option, alternative treatments are associated with a unique set of adverse effects which should also be considered when discussing these treatments with patients.

INTRODUCTION

Papular Urticaria (PU) is a hypersensitivity reaction to arthropod bites, most commonly mosquitoes, fleas, and bedbugs.[1,2] It is characterized by recurrent or chronic papules, pustules +/- wheals, and severity is dependent on the host response to the saliva and associated proteins released by the insect.[1]

EPIDEMIOLOGY

PU is a common encounter in dermatology outpatient clinics of tropical and sub-tropical regions, particularly in the spring and summer months, with the prevalence peaking after age 2 and tolerance developing in most children by age 10.[3] Recurrence is also noted to arise in the Fall and Winter months, requiring it to be included as a differential diagnosis during all seasons of the year.[2,3] In certain countries with a lack of a reliable water source, the practice of storing water in drums and pans may promote mosquito breeding and contribute to the prevalence of PU and other mosquito-borne illnesses such as dengue fever, malaria, zika, and chikungunya. Children are more predisposed to the condition, likely as a result of immature immune systems and behavioral/ social norms that facilitate exposure to the offending insects.[2] No sex predominance has been outlined in the general literature, however Raza et al demonstrated a male predominance (63.6%) in a case control study assessing 280 pediatric patients with PU.[1]

CLINICAL PRESENTATION

The lesions associated with PU tend to evolve. The presentation varies depending on the individual's lifetime exposure to the insect bite. Mellanby outlined this sequence after intradermal injection of mosquito antigens during the 1940s[4]:

> Stage I: Minimal reaction: this stage is associated with a period of sensitization during infancy.
> Stage II: Delayed type hypersensitivity (type IV) reaction
> Stage III: Immediate hypersensitivity (type I) urticarial papule followed by a delayed reaction
> Stage IV: Immediate reactions only (not delayed)
> Stage V: No reaction

Stage III indicates the individual's peak of sensitization.[4] Typically, the injection of foreign proteins into the skin may cause an immediate pruritic urticarial eruption which is succeeded by an indurated papule which may last several

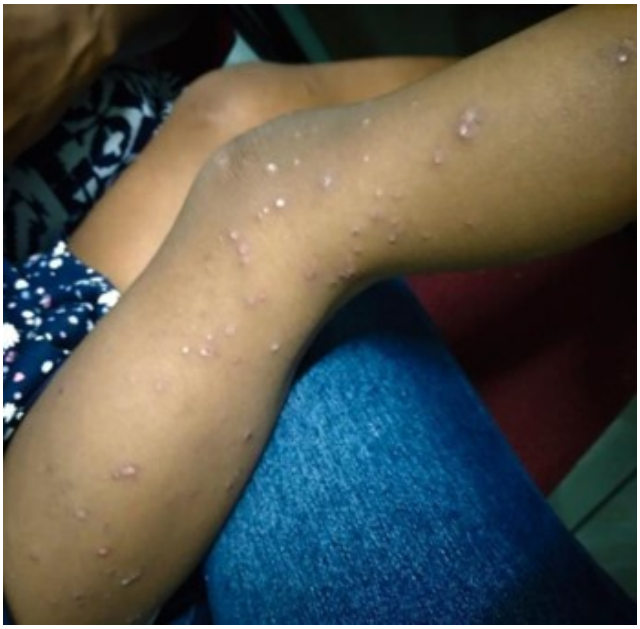

Figure 1. Extensive papular eruptions and excoriations on the distal limbs. The patient pictured had a clinical history of insect bites.

days. The wheal and papule may have a hemorrhagic central punctum. Lesions occur at irregular intervals and appear in clusters on exposed areas such as the distal limbs and constricting areas such as around the waistband or the top of socks. The latter presentation may be due to the diminished blood flow in these areas, possibly due to external pressure, which may enhance the precipitation of immune complexes.[3] PU eruptions may form bullous eruptions on the lower legs, and constant itching predisposes the patient to secondary eczematous changes and secondary infections.[5]

The delayed-type hypersensitivity response is the underlying mechanism for the variable chronicity and severity of the insect bite reactions in the pediatric population. The elapsed time between an insect bite and the eruption of a pruritic papule lengthens as children gain continued exposure to the antigens, in keeping with the stage III response. Consequently, it can become difficult for a patient and/or parent to accurately report "bite events." Additionally, a phenomenon known as "reactivation" can result in variable severity of pruritus and skin lesions even when the number of new lesions seems to be waning. This effect is likely secondary to circulating insect antigen stimulating cutaneous T cells in previously sensitized sites.[2] Clinical evidence of this is seen in children with generalized eruptions and pruritus after only limited exposure to biting insects at a focal site, which may last for a total of 4-6 weeks.[3] (Figure 1)

Recurrence of PU with re-exposure seems to lessen in adolescence and adulthood. This might reflect the development of immune tolerance towards the apposite antigenic proteins.

HISTOPATHOLOGY

Eosinophils were present in 86% of histopathology samples of patients with clinically diagnosed PU.[6] Jordaan et al therefore speculated that PU was primarily mediated through a type I hypersensitivity reaction. However, Garcia et al observed both a predominance of eosinophils and CD4 T-cells throughout the dermis in all lesions injected with flea antigens to induce PU.[7] This supports the hypothesis that both immediate and delayed hypersensitivity reactions are involved in the pathogenesis of PU.

CYTOKINES INVOLVED IN PAPULAR URTICARIA

The chemokines involved in the pathogenesis of pruritus, wound healing, and hypersensitivity responses have a large degree of overlap. The pruritus involved in PU is primarily skin-derived and consequently involves the C-nerve fiber, although there may be some neurogenic involvement.[8] Cuellar et al have succinctly described the immunopathogenesis of flea bite-induced papular urticaria (PUFB): while no significant difference was found between the patients and healthy controls with regard to plasmatic IL-4 and interferon (IFN) levels, polyclonal stimulation demonstrated that patients suffering from PU predominantly responded with Th2 cytokine production via releasing increased IL-4 secreting CD4+ cells compared to healthy controls ($p = 0.03$).[9] Additionally, the patients with PUFB were found to have lower levels of regulatory cytokines such as IL-10 ($p < 0.05$).[10] This may indicate that patients underwent an atopic stage that may have predisposed them to develop the disease ie the immunological response of PUFB has an allergenic origin.[9,10]

Similarly, excoriation secondary to incessant itching triggers wound healing and a subsequent cycle of inflammation begins. During the first stage of wound healing, keratinocytes are signaled to release prestored interleukin-1 (IL-1), a proinflammatory cytokine which stimulates a cascade response of additional inflammatory mediators and initiates the clotting cascade.[11] The resulting clot induces hemostasis and the degranulating platelets release alpha granules, which secrete growth factors such as epidermal growth factor, platelet derived growth factor, and transforming growth factor-beta (TGF-B), with the purpose of attracting neutrophils to the involved site.[11] IL-6, another pro-inflammatory cytokine, is then subsequently released by the macrophages converted from monocytes, which contribute to the inflammatory cascade.[11] Interestingly, IL-6 levels were found to be decreased in patients with PUFB in the study by Cuellar et al, which may indicate that the role of this proinflammatory cytokine in the pathogenesis of PUFB has yet to be elucidated.[10]

Understanding the immunological profile and interplay of various cytokines in PU provides the opportunity to seek treatments that can potentially address these irregularities. While they have not been studied specifically in the management of PU, it is possible that the immunomodulatory effects of garlic, turmeric, zinc, balneotherapy, quercetin, and rhododendron tomentosum may be extrapolated to its management.

METHODS

The recommendations in this review were developed by conducting an extensive literature search across PubMed, COCHRANE Database of Systematic Reviews, and Google Scholar. No restrictions on study type or date were applied. Keyword search terms were input in the search engines such as "papular urticaria," "pruritus," "complementary medicine," "integrative medicine," "immunomodulat*," "oral," and "topical."

Studies selected in this review highlighted the underlying immunology involved in the mechanism of action for aged garlic extract (AGE), curcumin, zinc, balneotherapy, and quercetin. We extrapolated this information to theoretical application in treatment of PU given the potential for immunomodulation of the PU inflammatory response. Rhododendron tomentosum was included for the potential benefit of repellency. The CAM agents in this paper were chosen from our experience and observations of alternative methods patients and providers have attempted to use.

ANTI-INFLAMMATORY ROLE OF GARLIC

Different dietary garlic formulations, such as powder distributed in the form of tablets, garlic oil distributed in capsules, and AGE distributed as tablets, capsules, and liquids have been incorporated into the globally increased market of garlic bioactive compounds.[12] AGE has been the most extensively studied formulation of garlic in dermatology literature and has more potent immunomodulatory effects than raw garlic.[13] The ingredients are alliin, cycloalliin, S-allyl-L-cysteine, S-methyl-L-cysteine, S-ethylcysteine, S-1-proponyl-L-cysteine, S-allylmercapto-L-cysteine, fructosyl-arginine, and beta-chlorogenin along with L-arginine, L-cysteine, and L-methionine.[12] Oral formulations have been shown to be effective in increasing cutaneous microcirculation, immunomodulation, as well as UVB protection and cancer treatment.[13,14]

Regarding immunomodulation, AGE enhances the immune response via release of IL-2, TNF- α, and IFN- γ, and enhances natural killer cell and lymphokine-activated killer cell activity.[13] This shift towards Th1 is in keeping with Liu et al's finding that supplemental garlic oil has a dual effect on Th1-Th2 cell balance: an enhanced T cell response towards the Th1 type is observed at low doses (50 mg/kg) and towards the Th2 type at high doses (200 mg/kg).[15] This finding was demonstrated in an in vivo rat model after two weeks of administration of varying concentrations of garlic oil.[15] The Th1 properties may be beneficial for wound healing as allicin treatment stimulates the expansion of CD4+ T cells and macrophages.[12] As PU has varying hypersensitivity responses, the dose of garlic extract could potentially be individualized according to the patient's current stage in disease evolution. For example, patients with a stage II delayed type hypersensitivity response may benefit from high doses, while those with a stage III immediate hypersensitivity response may benefit from low dosage. This theory is supported by Kyo et al's findings of decreasing antigen-specific histamine release (50% decrease with 1.5 g/ 100 g AGE vs 90% decrease with 5 g/ 100 g AGE) with murine oral supplementation of AGE, a finding that was observed in in vitro rat models after one hour of incubation with AGE.[16] Arreola et al also supported decreasing immunoglobulin E-mediated skin reactions after supplementation with increasing oral AGE, as measured by decreased spongiotic changes in the ears of murine models noted at 4 and 24 intervals.[16]

ANTI-INFLAMMATORY ROLE OF TURMERIC

Turmeric (Curcuma longa) is a spice with anti-inflammatory properties. Its active ingredient, curcumin, is a strongly hydrophobic compound that has poor bioavailability, which poses challenges in oral ingestion.[17] Curcumin has been demonstrated to modulate the activation of T cells, B cells, and macrophages, downregulate various proinflammatory cytokines and chemokines, and enhance antibody responses. IL-2 production and the development of cytotoxic T lymphocytes is irreversibly suppressed at 12.5-30 μmol/L curcumin, with the effect on the latter being greater.[18] Furthermore, recently it has been shown that curcumin inhibits IL-12 production in macrophages in a dose-dependent manner, leading to the inhibition of Th1 cytokine profile in CD4+ T cells, suggesting that a variety of biological effects of curcumin also include anti-inflammatory activity.[19,20] The main limitation of curcumin use is its poor bioavailability due to limited absorption, fast metabolism, and rapid elimination from the body.[17] The addition of black pepper, and use of liposomal curcumin, nanoparticles, and phospholipid complexes are a few techniques that have allowed for increased bioavailability of curcumin.[21]

ANTI-INFLAMMATORY ROLE OF ZINC

Thymulin, a zinc dependent hormone secreted from the thymic stroma, governs T cell proliferation, cytokine production, and expression of IL-2 receptors on T cells. This hormone is biologically inactive when zinc is deficient and its receptors are highly specific for the zinc ion.[22]

With the supplementation of zinc, Mohamed et al demonstrated significant stimulation of IFN- γ and decreased IL-10 production (non-statistically significant) from peripheral blood mononuclear cells in vitro in blood samples drawn from atopic patients.[23] The non-significant decrease in IL-10 may be due to increased regulatory T cells, as T reg cells produce IL-10.[24] These findings are important as children with PU frequently have overlapping atopic diseases, and as such, the supplementation of zinc could potentially shift the cytokine profile away from the predominant Th2 release seen in atopy, and decrease the severity and frequency of relapses. Furthermore, the shift towards a Th1 profile, as evidenced by the stimulation of IFN- γ would theoretically decrease the immediate-type hypersensitivity reactions (which involve the release of IL4, IL-13, and IgE) associated with insect bites, and therefore decrease the likelihood of sensitization in a patient. However, the implications of increasing the stage 2 delayed type IV hypersensitivity reaction needs further exploration.[23] Of note, the different levels of zinc observed in adult atopic asthmatic patients vs adult non- atopic asthmatic patients

in the study by Mohammed et al were 54.94 (μg/dL) ± 10.38 vs. 95.77(μg/dL) ± 6.81, respectively ($p < .001$). Therefore, patients with atopy were more likely to have lower zinc levels, regardless of symptom status.[23] As both asthma and PU are on the atopic spectrum, studying zinc levels in PU may be useful.

There are no studies known to us which look specifically at the effect of zinc supplementation on pruritus in PU. In this study by Mapar et al, treatment of uremic pruritus with oral zinc sulfate at a dose of 220 mg/day for four weeks resulted in resolution of the pruritus in 4 out of 36 patients in comparison to a placebo group in which only one person had resolution of pruritus. The result, however, was not statistically significant.[25] A major issue with this study is the very small sample size which is potentially responsible for the statistically insignificant findings. Also, the resolution of pruritus occurred after 4 weeks which is approximately the time in which PU eruptions and pruritus would be expected to resolve regardless. A more rapid onset of pruritus relief would be needed for usefulness in the management of PU. Finally, this dose of zinc may be intolerable to a wider patient population and the findings may not be similar in pruritus secondary to PU.

BALNEOTHERAPY

Balneotherapy is the practice of immersing an individual in a thermal mineral water bath to gain anti-inflammatory benefits. This bath may contain sulfates, chloride, bicarbonate, or slightly mineralized trace-metal, and may vary in temperature. An artificial balneotherapy can be arranged for the treatment of inflammatory skin diseases like PU. Salt baths with concentrations up to 30% and temperatures from 30-35ºC are ideal and phototherapy may be added to the treatment for potentiation of the anti-inflammatory effect (balneophototherapy).[26]

The proposed immunomodulatory effects of balneotherapy are thought to vary depending on the components of the mineral water. For instance, an indirectly proportional decrease in T-cell expansion and cytokines such as IL-2 and IFN-γ is noted with increased concentration of sulfur spring water in patients undergoing balneotherapy for atopic dermatitis. Artificially created salt water baths may have a similar mechanism of action. However, some degree of placebo effect from the thermal component of the bath may also play a role in the efficacy of treatment.[26]

The efficacy of balneotherapy on pruritus and xerosis using natural mineral water sources such as the Dead Sea and La Roche-Posay have been studied using clinical trials. Efficacy was as high as 90% after 4-6 weeks in a study of 1408 patients with a diagnosis of atopic dermatitis undergoing balneotherapy at the Dead Sea.[26]

No major adverse effects are expected with balneotherapy. However, highly concentrated salt solutions may cause a burning sensation and/or pruritus when in contact with open and weeping lesions. Additionally, balneotherapy may be a challenge to access as it requires set conditions and a bath or pool for body immersion, which many affected persons may not have access to.

QUERCETIN

Quercetin is a naturally occurring anti-inflammatory polyphenol belonging to the flavonoids family that has been used in the management of inflammatory skin disease. Quercetin attenuates the inflammatory response through the downregulation of nuclear factor kappa B (NF-kB) and p38 mitogen-activated protein kinase (MAPK) in mast cells and suppression of serum IgE, eosinophils, IL-4, IL-5, and IL-13 as well as proinflammatory cytokines and other molecules involved in inflammation.[27]

A single blind study by Maramaldi et al investigated the anti-itch effect of a quercetin containing cream applied topically in 30 healthy participants. The 1% quercetin containing cream was compared to no product, placebo, and a positive control containing 1% dexchlorpheniramine. The quercetin compound and dexchlorpheniramine were effective in improving erythema -10.05% ($p=0.00329$) and -14.05% ($p = 0.00046$) respectively. Wheal diameter and pruritus had also decreased with both agents.[28]

Quercetin in its natural state does not readily penetrate the skin, hence an appropriate vehicle is paramount to extracting the benefits. In the above study, a phospholipids-based delivery system was used. Unlike many natural therapeutic compounds, there are no significant adverse effects noted with quercetin.[28] The anti-inflammatory and anti-pruritic effect of quercetin therefore makes it a reasonable option for the management of PU, perhaps in a similar formulation of quercetin 1% phospholipid-based cream.

RHODODENDRON TOMENTOSUM (LEDUM PALUSTRE)

Rhododendron tomentosum (Ledum palustre), also known as northern Labrador tea, is known to have insecticide properties and may be used as a natural insect repellent for various species. Laboratory tests by Jaenson, Palsson, and Borg-Karlson have established the repellent effects of the ethyl acetate extract of Ledum palustre against Aedes aegypti L. mosquito.[29] Another lab test by the same authors revealed that Ledum palustre, when formulated into an essential oil and diluted in 10% acetone showed almost complete repellency (95%) against the Ixodes ricinus tick. Ethyl acetate extract demonstrated less repellency (70%) against Ixodes ricinus. Diethyltoluamide (DEET) which is present in most commercially sold insect repellents has a similar efficacy to the Ledum palustre essential oil formulation. This finding may serve to promote Ledum palustre as a valid alternative to those who are averse to using DEET-containing repellents.

Adverse effects of ledol in Ledum palustre essential oil in low doses are minimal. However, in high doses over a prolonged period, dizziness, nausea, vomiting, paralysis, loss of consciousness, and even death can occur.

Standardized formulations for Ledum palustre have not been determined, although various commercial formulations exist online.[30]

The immunomodulatory mechanisms of the featured CAM agents

CAM Agent	Mechanism of Action	Dosing	Side Effects
Aged Garlic Extract	Increased IL-2, TNF- α and IFN- γ, enhances natural killer cell and lymphokine-activated killer cell activity.[13]	Low doses (50 mg/kg); enhanced T cell response towards the Th1 type High doses (200 mg/kg): enhanced effect and towards the Th2 type.[15]	Increased risk of bleeding.[31]
Curcumin	Regulation of neutrophils, inhibition of IL-2 production and the development of cytotoxic T lymphocytes.[18] Inhibition of IL-12 production in macrophages in a dose-dependent manner, leading to the inhibition of Th1 cytokine profile in CD4+ T cells, downregulation of the activation of the transcription factor NF-kB.[19,20]	Doses range from 500 mg daily to up to 2600 mg daily.[32] Piperine or other modification should be added to increase bioavailability.	Increased risk of bleeding.[31]
Zinc	Stimulation of IFN- γ and decreased IL-10 production.[23]	Oral zinc sulfate at a dose of 220 mg/day has demonstrated efficacy in patients with uremic pruritus.[25]	Excessive intake may result in headache, GI upset.[33] Also, cross reaction with tetracycline, quinolone, and thiazide diuretics.[34]
Balneotherapy	Decrease in T-cell expansion and cytokines such as IL-2 and IFN-γ (sulfur spring water).[26]	Varies based on source. Artificial salt water baths up to 30% concentration, 30-35ºC.[26]	Burning sensation or pruritus when in contact with open skin.[26]
Quercetin	Attenuates the inflammatory response through the downregulation of NF-kB and p38 MAPK in mast cells and suppression of serum IgE, eosinophils, IL-4, IL-5, and IL-13.[27]	Potentially 1% phospholipid based cream.[28]	-
Rhododendron tomentosum (Ledum palustre)	Natural insect repellent comparable to DEET.	No standardized dose, various formulations and doses available commercially.	Dizziness, nausea, vomiting, paralysis, loss of consciousness, and even death can occur when exposed to high doses.[30]

PREVENTATIVE MEASURES FOR PAPULAR URTICARIA

Typically, the management of PU begins with educating patients or parents on the diagnosis as well as identifying and removing the causative agent. In areas with a high mosquito burden, patients are advised to use mosquito nets, protective clothing, insect-repellent and to take measures such as covering water storage containers and removing stagnant collections of water around the home.[35] When a bedbug infestation is suspected, fumigation of the home and hygiene measures are recommended. Medications such as topical permethrin are traditionally used concomitantly to ensure extermination of the insects. Pets should also be examined for fleas.[36]

SUMMARY

In developing countries with limited access to conventional treatment options for PU, alternative treatments may be welcomed from not just a financial standpoint but also from a cultural one. In the US and UK, botanicals and alternative medicine have become increasingly popular and there are patients who may be more inclined to choosing these options. It is important to note that none of the agents discussed have been studied in PU. We have explored their potential use based on evidence of modulation of the inflammatory pathways imbalanced in PU. Additionally, PU primarily affects children, and none of the studies discussed included children, again highlighting the fact that this is a theoretical exploration of potential agents that has no clinical application and requires further study before any of the agents can be considered.

DISCLOSURES

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