Evaluation of efficacy and safety of Purim Tablets in chronic dermatitis, with special reference to atopic dermatitis

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ABSTRACT
Dermatitis is a commonly encountered skin inflammation with variable etiology and clinical presentation. Available treatment options for dermatitis management have a major drawback of failure in prevently high recurrence and chronic dermatosis are characterized by recurrent exacerbations and remissions. This study was planned to evaluate the clinical efficacy and short- and long-term safety of Purim tablets in chronic dermatitis, with special reference to atopic dermatitis.

This was an open non-comparative clinical trial and total fifty patients, who were refractory to conventional treatment and who were willing to give informed consent, were included in the study. Pregnant and lactating women, children below 14 years of age, patients with severe systemic illness and patients with genetic disorders were excluded from the study.

At the initial visit, a detailed medical history, with special emphasis on family history of atopy, history of known contacts and treatment history was obtained from all patients. Duration of symptoms, onset status, recurrence, anatomical distribution, initiation of lesion, pain and presence of any additional signs was noted. The details of present episode were recorded in terms of onset, progression of the lesion, relieving factors and seasonal exacerbation. The local examination included details of the pattern and morphology of the lesion. Each symptom was given equal weightage on a specially designed score scale and the total score was calculated before and after the drug treatment. All the included patients were advised to consume Purim tablets, at a dose of 2 tablets, twice daily, for a period of six weeks.

The patients were followed up for 6 weeks and score evaluation was recorded at the end of each week and a complete clinical and hematological examination was done at the end of the 6th week. All adverse events either reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. The predefined primary end points were reduction in the mean scores of dermal edema, pruritus, papules, vesicles, urticaria, tenderness, epidermal thickening, scaling and pigmentation. The predefined secondary end points were incidences of short- and long term adverse events and compliance to the drug treatment. Statistical analysis was done according to intention-to-treat principles. Changes in various symptomatic parameters from baseline values and values after the 2, 4 and 6 weeks were analyzed by “Wilcoxon sign Rank test”.

The minimum level of significance was fixed at 95% confidence limit and a 2-sided \( p \) value of \(<0.005\) was considered significant.

The mean score for fissuring, excoriation, papules, hyper- and hypo-pigmentation, oozing, erosion, maceration, plaques, scaling and xerosis reduced significantly at the end of 2, 4 and 6 weeks period. There were no clinically significant adverse events reported and observed during the entire study period. This clinical trial observed highly significant rapid symptomatic relief and clinical improvement, with Purim tablets. This study concludes that, Purim tablets are clinically highly effective and safe in all types of chronic dermatitis.

INTRODUCTION

Dermatitis, also referred to as eczema, is a commonly encountered skin inflammation and generally, dermatitis describes swollen, erythematous and itchy skin. The etiology and clinical presentation varies with the subtypes of dermatitis. Contact dermatitis appears within minutes of exposure to an allergen, and is clinically seen as localized erythema, itching, and blisters. Neurodermatitis (lichen simplex chronicus) is a result of repeated scratching, with apparent patches of thickened, brownish skin with lichenified margins. Seborrheic dermatitis (itchy dandruff, cradle cap) is seen as a greasy, scaling area/s appearing on nose, in-between eyebrows, behind ears or over breastbone. Stasis dermatitis is associated with varicose veins and the skin at ankles and over shins, becomes discolored (red or brown), thick and itchy, with occasional ulcers. Perioral dermatitis is common in young women, resembling similar to acne; causing small red, pus-filled bumps or mild peeling. Atopic dermatitis (AD), infantile eczema, is seen as itchy, thickened, scaly skin in the folds of elbows, backs of knees, on face, hands and feet. AD has been called “the itch that erupts”, rather than “the rash that itches”\(^1,2\).

Available treatment options for dermatitis management have major drawback of failure in prevent high recurrence and chronic dermatosis are characterized by recurrent exacerbations and remissions. Contact dermatitis recurs due to practical difficulties in avoiding of irritants. In the treatment of neurodermatitis, getting the patient rid off the scratching habit to avoid skin aggravation is hard and use of antihistamines, corticosteroids, sedatives or tranquilizers is associated with the risk of habituation. In seborrheic and stasis dermatitis, secondary infections are frequent. Perioral dermatitis recurrence is common with stoppage of topical corticosteroid treatment. Though immunomodulators (in conjunction with corticosteroids, astringents and antihistamines) reduce flares of atopic dermatitis, the recurrence rate is high\(^2\).

Purim tablet is a polyherbal formulation indicated for management of chronic dermatitis and it contains extracts of \textit{Curcuma longa}, \textit{Cassia fistula}, \textit{Psoralea corylifolia}, \textit{Saussurea lappa}, \textit{Picrorhiza kurrooa}, \textit{Azadirachta indica}, \textit{Tinospora cordifolia}, \textit{Crataeva magna}, \textit{Eclipta alba}, \textit{Andrographis paniculata}, \textit{Emblica ribes}, \textit{Emblica officinale}, \textit{Terminalia chebula} and \textit{Terminalia belerica}. This study was planned to evaluate efficacy and safety of Purim tablet in chronic dermatitis.

Aim of the Study

The aim of the study was to evaluate the clinical efficacy and short- and long-term safety of Purim tablets in chronic dermatitis, with special reference to atopic dermatitis.

Study Design
This was an open non-comparative clinical trial, conducted from October 2001 to April 2003, at the Department of Dermatology, L.T.M.M. College & L.T.M.G. Hospital, Sion, Mumbai, India and was approved by the Institutional Ethics Committee.

MATERIALS AND METHODS

Subjects
Total fifty pediatric and adult patients, with clinical symptoms of dermatitis were included in the study.

Inclusion Criteria
Clinically diagnosed patients of chronic dermatitis, who were refractory to conventional treatment and who were willing to give informed consent, were included in the study.

Exclusion Criteria
Pregnant and lactating women, children below 14 years of age, patients with severe systemic illness and patients with genetic disorders were excluded from the study.

Study procedures
At the initial visit, a detailed medical history, with special emphasis on family history of atopy, history of known contacts (irritants: cosmetics, perfumes, and deodorants; clothing: synthetic, wool; rubber and plastic objects; clips, buttons, elastic, leather, plants; foods: egg, shellfish, citrus fruits; drugs: antibiotics, antiseptics, local anesthetics; metals: jewelry, prosthesis, beryllium: fluorescent light, wood, toys, and others: cement, chemicals, insecticides). The treatment history (drugs and impact of treatment) was obtained from all patients. Duration of symptoms (6 months/1 year), onset status (acute/gradual onset), recurrence, anatomical distribution (generalized/localized), initiation of lesion (papule/urticaria/pinpoint hemorrhage), pain (tenderness/numbness) and presence of any additional signs (blisters/pustules) was also noted.

The details of present episode was recorded in terms of onset (sudden, gradual and exacerbation of pre-existing lesions), progression of the lesion (progressive, recurrent or static), relieving factors (work absenteeism, home rest or any other) and seasonal exacerbation was recorded. In all patients, a thorough systemic examination was done, which was followed by a detailed local examination of the involved area. The local examination included details of the pattern of the lesion (localized, generalized, unilateral, bilateral or photoexposed), morphology of the lesion (oozing, erosion, maceration, fissuring, excoration, papules, plaques, scaling, xerosis, hyper- and hypopigmentation and urticaria. Each symptom was given equal weightage on a specially designed score scale, and each score was rated as 0 (if there were no symptoms), 1 (presence of mild symptoms), 2 (presence of moderate symptoms) and 3 (presence of severe symptoms). The total score was calculated before and after drug treatment.

All the included patients were advised to consume Purim tablets, at a dose of 2 tablets, twice daily, for a period of six weeks. The total duration of the study was three months.
The overall assessment of tolerability was based on the reported and observed adverse events and graded as good (no adverse effects), fair (mild to moderate adverse effects) and severe (adverse effects requiring withdrawal of the treatment). The patients were asked to grade the efficacy of the drug treatment in the predefined grades as: excellent (90-100% improvement), good (75-90% improvement), fair (50-75% improvement) and poor (<50% improvement).

Follow-up and assessment
Patients were followed up for 4 weeks and score evaluation was recorded at the end of each week and a complete clinical and hematological examination was done at the end of the 4th week.

Adverse events
All adverse events either reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Primary and secondary end points
The predefined primary end points were reduction in the mean scores of dermal edema, pruritus, papules, vesicles, urticaria, tenderness, epidermal thickening, scaling (size, excoriation, exudation, pin point hemorrhage and weeping exudation) and pigmentation. The predefined secondary end points were incidences of short- & long term adverse events and compliance to the drug treatment.

Statistical analysis
Statistical analysis was done according to intention-to-treat principles. Changes in various symptomatic parameters from baseline values and values after the 2, 4 and 6 weeks were analyzed by “Wilcoxon sign Rank test”. The minimum level of significance was fixed at 95% confidence limit and a 2-sided \( p \) value of <0.005 was considered significant.

RESULTS
Total fifty patients were enrolled in the study and 4 patients were lost to follow up. The mean age of all patients was 42.69 years (SD = 15.65, range = from 13 to 70 years) and there was a male preponderance in the
study (32 males and 18 females). The mean duration of lesions were 3.8 years. 18 (36%) patients had sudden onset of the dermatitis and in 30 (60%) patients, the onset was gradual. In 2 (4%) patients, there was exacerbation of preexisting lesions. Itching was the most predominant complaint (96%) reported by the patients, followed by dryness (72%), fissuring (40%), oozing (36%), erosion (36%), burning sensation (28%), pain (10%) and maceration (4%) (Figure 1). In this study, 16% of total cases had suspected contact of detergents and soaps, 14%, household products, 4%, cosmetics (hair bleach, deodorants and perfumes), jewelry and medicaments (2%). In 12 (24%) patients, there was no reported association between any suspected contacts (Figure 2). The Pattern of lesion is as shown in Figure 3.

The mean score for fissuring reduced from 1.08 to 0.88, 0.54 ($p<0.05$) and 0.34 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for excoriation reduced from 1.60 to 0.88, 0.47 ($p<0.05$) and 0.31 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for papules reduced from 2.22 to 2.06, 1.52 ($p<0.05$) and 1.01 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively (Figure 4).

The mean score for hyperpigmentation reduced from 2.06 to 1.94, 1.40 ($p<0.05$) and 1.04 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for hypopigmentation reduced from 0.26 to 0.18 ($p<0.05$), 0.16 ($p<0.05$) and 0.06 ($p<0.05$), at the end of 2, 4
Similarly, the mean score for oozing reduced from 0.54 to 0.34, 0.04 ($p<0.05$) and 0.02 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for erosion reduced from 0.96 to 0.63 ($p<0.05$), 0.24 ($p<0.05$) and 0.14 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for maceration reduced from 0.02 ± 0.14 to 0 at the end of 2nd week (Figure 6).

The mean score for plaques reduced from 2.08 ± 1.12 to 1.86 ± 1.11, 1.52 ± 1.01 ($p<0.05$) and 1.30 ± 0.93 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for scaling reduced from 2.30 ± 1.20 ($p<0.05$), 1.49 ± 0.59 ($p<0.05$) and 0.56 ± 0.86 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively. The mean score for xerosis reduced from 1.72 ± 1.59, to 1.14 ± 1.53 ($p<0.05$), 0.60 ± 0.33 ($p<0.05$) and 0.26 ± 0.06 ($p<0.05$), at the end of 2, 4 and 6 week periods, respectively (Figure 7).

There were no clinically significant adverse events reported and observed during the entire study period. In the subjective evaluation of the drug treatment, 2 (4.3%) found
the treatment excellent, 25 (54.3%) found it good, 13 (28.3%) found it fair and 6 (13.1%) rated the treatment as poor (Figure 8). The compliance to the treatment was good for 36 (78.3%) patients and fair for 10 (21.7%) patients (Figure 9).

**DISCUSSION**

Although newer treatment options have changed the natural history of dermatitis, amongst all types of dermatitis, atopic dermatitis is the most difficult to treat. Atopic dermatitis is a syndrome with its variable clinical presentations and prognosis, and the estimated prevalence of AD varies between 10 and 30%. The increase in atopic disease has been rationalized by a "hygiene hypothesis," which attributes the propensity toward the atopic diseases to reduced microbial exposure in early life (especially in developed countries). Parental history of atopy or eczema is the strongest risk factor for atopic dermatitis and maternal atopy is a greater risk for atopic disorders in offspring than paternal atopy. The prevalence of AD is inversely related to the number of siblings and the larger the family size, the less the likelihood of having AD.

In 1923, Coca and Cooke coined the term "atopy" to describe the clinical presentations of type I hypersensitivity, which they noted in patients with asthma, hay fever, eczema, urticaria, and food allergies, but with recent immunologic advances, this definition has become insufficient. Lack of an updated official definition of AD is a major obstacle in reaching a consensus regarding the diagnosis of AD; as non-allergists recognize atopy in those patients with a family or personal history of asthma, hay fever, or eczema, while allergists recognize atopy as epiphenomena of immunologic aberrations, distinctive to a genetically predisposed population.

The most commonly recognized triggers of itch are exposure to heat, increased perspiration, woolen cloths, emotional stress, alcohol, house dust mites, xerosis, detergent and disinfectant soaps, contact with fresh fruits juices, meat and vegetable, occupational exposure to chemicals and fumes, pets (cats, dogs, birds), seasonal pollens and molds, human dander ("dandruff"); microorganisms (Staphylococcus aureus works as a "superantigen"); viruses (respiratory syntactical viruses (RSVs)), fungi like Pityrosporum, Candida, and dermatophytes, change in climate, certain type of food, personality type, and hormones.
Increased staphylococcal skin colonization of affected and normal skin has been noted in patients with AD compared with controls\textsuperscript{26}, although the majority of patients with AD are colonized by \textit{Staphylococcus aureus}, antibiotic treatment is indicated only when there is evidence of overt clinical infection or a suspected ‘superantigen effect’\textsuperscript{27}. The presence of \textit{Pityrosporum ovale}-specific IgE antibodies has been found in 49\% of patients with AD\textsuperscript{28}. Some viral skin infections (herpes, varicella, Epstein-Barr virus, parainfluenza virus, RSVs and cytomegalo virus) can have a drastic course\textsuperscript{29,30}. Ingested vasodilatory agents such as alcohol\textsuperscript{31}, spices, hot drinks and histamine-containing foods such as cheese, and ripe vegetables (tomatoes, spinach) can all cause dry flushing leading to pruritus\textsuperscript{2,32}.

Atopic patients have an abnormal pattern of thermoregulation, which is believed to reflect an intrinsic disturbance of the parasympathetic system, which also influences the activity of AD\textsuperscript{33}. Most patients are aware of seasonal variations and most patients experience improvement in summer with worsening in winter\textsuperscript{21}, however, heat- and exercise-induced sweating can trigger an exacerbation at anytime of the year\textsuperscript{34}. One third of young female patients reported premenstrual flare-ups of their AD\textsuperscript{25}. Vaughn-Jones \textit{et al.} in a study of pregnant women found a surprisingly high prevalence of eczema with a significant reduction in serum cortisol levels\textsuperscript{2,35}.

Pruritus, the most disturbing symptom, is considered an innate perception of mild mechanical stimulation as “itch” and “not as touch”\textsuperscript{34}. Once the pruritus begins, the surrounding skin becomes hyper-reactive to lighter stimuli with itch and this phenomenon is termed as “Allokinesis” or “Twitchy Skin Syndrome”. The sub- and intra-epidermal free nerve endings in patients with AD is normal, but Urashima \textit{et al.} found an increased density, diameter and number of axons, in each nerve fiber of the cutaneous nerves\textsuperscript{36}. Several neuropeptides have been identified as potent inducers of pruritus and vasodilation of the affected skin\textsuperscript{37}. Scratching the skin releases ‘Substance P’ from cutaneous proprioceptor nerves, which induces the release of histamine from mast cells in the scratched area and elevated concentrations of histamine are found in the skin and plasma of patients with AD\textsuperscript{38}. Not all patients with AD will be triggered by each stimulus and there are subsets of patients with AD who will experience exacerbations by specific triggers only\textsuperscript{2}.

A clinically useful set of criteria for the diagnosis of AD include atopy, pruritus, eczema, and altered vascular reactivity. As the histology of eczema is nonspecific, eczema is a clinical symptom and not a specific diagnosis. All eczemas are histologically spongiotic, but not all spongiotic dermatoses are eczematous. Clinically, the eczema is polymorphic, with acute (oozing, crusted and eroded microvesicles on erythematous papular plaques), subacute (thicker, paler and scaly, erythematous excoriated plaques), and chronic (lichenified, scaly, hyperpigmented and excoriated papular plaques) forms\textsuperscript{2,39}.

The clinical spectrum of AD consists of eyelid dermatitis\textsuperscript{40}, pityriasis alba\textsuperscript{41}, cheilitis, nipple dermatitis\textsuperscript{42}, infra-auricular, retro-auricular, and infra-nasal fissuring\textsuperscript{43}, vulvar dermatitis and xerosis\textsuperscript{44}, keratosis pilaris\textsuperscript{45}, ‘allergic shiners’ (periorbital darkening), ‘Dennie-Morgan lines’ (symmetrical prominent folds, extending from the medial aspect of the lower lid)\textsuperscript{56}, vernal conjunctivitis (severe bilateral, recurrent, chronic inflammatory processes of the upper eyelid conjunctiva) and atopic keratoconjunctivitis\textsuperscript{47}, keratoconus (conical deformity of the cornea), palmar and plantar hyperlinearity (exaggerated dermatoglyphics of the palms and soles), periorbital milia (intraepidermal inclusion cysts resulting from the plugging sebaceous ducts) and anterior neck folds (horizontal folds running across the middle of the anterior neck)\textsuperscript{2}. 
Atopic dermatitis is the expression of polygenic and phenotypic immunologic malfunction, which manifest as a spectrum of inflammatory reactions mediated by the cytokines (IL-5, IL-4, IL-13, and IL-3) induced by T helper 1 (Th1) / Th2-cells, along with an increase in eosinophils, mast cells and IgE levels. Akdis et al. postulated that the cutaneous lymphocyte antigen receptors on the surface of the Th2 cells induce influx of inflammatory chemomediators into the skin in AD. The pathophysiology of the itch in AD is still not fully understood. Proteases, kinins, prostaglandins, neuropeptides, acetylcholine, cytokines, and opioids can potentiate histamine release when injected into atopic skin. Therefore, the most effective antipruritics in AD are systemic immunomodulators, glucocorticoids, cyclosporin A, calcineurin inhibitors, and ultraviolet light therapy. Although antileukotrienes, opioid antagonists, topical cromolyn and NSAIDs have been reported to be helpful in patients with AD, inconsistent results deter physicians from prescribing them routinely.

In the present study, there was rapid symptomatic relief from itching, dryness, fissuring, oozing, erosions, burning sensation, pain and maceration. There was significant reduction in the mean score for fissuring, excoriation, papules, hyper- and hypo-pigmentation, plaques, scaling and xerosis, at the end of the study period. There were no clinically significant short- and long-term adverse events, either reported or observed, during the entire study period, which indicates the dependable safety profile of the study drug. There were no exacerbations of preexisting lesions in all patients. The excellent outcome observed in these study patients might be due to the synergistic mechanism of action of all the ingredients of Purim tablets.

Curcuminoids, a group of phenolic compounds isolated from the roots of Curcuma longa, have anti-inflammatory, antioxidant and antimicrobial activities. In a study, the antioxidant effect of curcumin was demonstrated, and it was postulated that the antioxidant actions of curcumin were due to inhibition of Ca2+ entry and PKC activity. Curcuma longa shows NO-dependent vascular smooth muscle relaxation. Miquel et al. documented that in daily intake, Curcuma longa leads to potent anti-atherogenic effect (potentiating the anti-atherogenic effect of alpha-tocopherol) and antioxidant activity. Curcumin has been demonstrated to be safe in six human trials and it exerts its anti-inflammatory activity by inhibition of a number of different molecules that play a role in inflammation. Hong et al. demonstrated that the active extract of Curcuma longa mediates COX-2 and iNOS inhibitory activities. The capacity of curcumin to inhibit both cell growth and death strongly implies that these two biological processes share a common pathway at some point and that curcumin affects a common step, presumably involving a modulation of the AP-1 transcription factor. By use of X-ray diffraction and mass spectrometry, it was found that an unoccupied electron mass that appears to be an unusual degradation product of curcumin (4-hydroxyperoxy-2-methoxyphenol) and curcumin inhibit lipoygenase 1 (LOX1) by binding to its central cavity, and curcumin after binding to these PC micelles acts as a LOX1 inhibitor. Curcumin has been shown to inhibit experimental carcinogenesis, mutagenesis and suppression of COX-2 expression by inhibiting ERK activity and NF-kappaB activation may represent molecular mechanisms. In vitro, curcumin inhibited LPS-induced production of TNF and IL-1 by monocyctic macrophages.

Mani et al. observed an enhancement in wound repair and regulatory effect on transforming growth factor-beta (TGF-beta1), its receptors and iNOS in macrophages, by curcumin. Tissue repair and wound healing are complex processes that involve inflammation, granulation and tissue remodeling. Interactions of different cells, extracellular matrix proteins and their receptors are involved in wound healing, and are mediated by cytokines and growth
factors. In one study, wounds treated with curcumin showed earlier re-epithelialization, improved neovascularization, increased migration of cells (dermal myofibroblasts, fibroblasts, and macrophages) into the wound bed, and higher collagen content. Immunohistochemical localization showed an increase in transforming growth factor-beta1 and enhanced transforming growth factor-beta1 mRNA expression, in curcumin-treated wounds was confirmed by in situ hybridization, and laser scan cytometry. The curcuminoids from *Curcuma longa* synergistically inhibited nitroblue tetrazolium reduction and decrease in superoxide radical formation leading to lower levels of cytotoxic hydrogen peroxide was proposed as an explanation of its cutaneous-protective effect. *Azadirachta indica* and *Curcuma longa* have been used in a paste to heal chronic ulcers and Charles *et al.* observed a high cure rate within a few days of treatment without toxic or adverse reaction. Curcumin also acts as an immunostimulator, and increased circulating antibody titre, splenic plaque forming cells (PFC), alpha-esterase positive cells, and macrophage phagocytic activity, was reported. Curcumin inhibits Th1 cytokine profile in CD4+ T cells by suppressing IL-12 production in macrophages.

A meroterpenne and four flavonoids, bakuchiol, bavachinin, bavachin, isobavachin and isobavachalcone, were isolated from the seeds of *Psoralea corylifolia* as antioxidative components. These phenolic compounds in *Psoralea corylifolia* were shown to be effective in protecting biological membranes against various oxidative stresses. In one study, significant antibacterial activities by psoralidin, bakuchin, psoralin and angelicin (isolated from the seeds of *Psoralea corylifolia*) against a number of Gram (+) and Gram (-) bacteria were recorded. *Psoralea corylifolia* contains the active compound flavonoid, 4'-methoxy flavone. Rajendraprasad *et al.* demonstrated potent antifungal activity of *Psoralea corylifolia* against Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum and Microsporum gypseum. Bactericidal effects of bakuchiol against Staphylococcus aureus, Streptococcus mutans, Streptococcus sanguis, Streptococcus salivarius, Streptococcus sobrinus, Enterococcus faecalis, Enterococcus faecium, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Actinomyces viscosus and Porphyromonas gingivalis, were reported. In another study, *Psoralea corylifolia* was found to stimulate natural killer cell activity and antibody-forming cells. *Psoralea corylifolia* was also found to inhibit the aggregation of platelets induced by arachidonic acid, collagen, and platelet activating factor. One study recorded that *Psoralea corylifolia* caused strong DNA polymerase inhibition specific for inhibitors of DNA replication enzymes.

Various studies reveal that the extracts of *Saussurea lappa* possess anti-inflammatory activity. Costunolide, a sesquiterpene lactone isolated from the root of *Saussurea lappa*, is known to have anti-fungal activities. The inhibitory effect of costunolide on the protein and mRNA expression of IL-1beta was demonstrated by suppressing the transcriptional activity of the IL-1 beta promoter, along with inhibition of the activity of AP-1 transcription factor, and phosphorylation. The studies suggest that the anti-inflammatory activity of the sesquiterpene lactone fraction of *Saussurea lappa* is due to stabilization of lysosomal membranes and an antiproliferative effect. Cho *et al.* investigated anti-inflammatory effects of cynaropicrin, a sesquiterpene lactone from *Saussurea lappa*, and reported strong inhibition of TNF-alpha release from macrophages, potent attenuation of the accumulation of NO release, and suppression of the proliferation of lymphocytes. Cynaropicrin participates in the inflammatory response by inhibiting the production of inflammatory mediators and the proliferation of lymphocytes and its inhibitory effect is mediated through conjugation with sulphydryl groups of target protein(s). Lee *et al.* reported an inhibition of cytokine induced neutrophil chemoattractant (CINC), an IL-8, in peritoneal macrophages. The
methanolic extract of *Saussurea lappa* was reported to potently inhibit LPS-induced NO production in LPS-activated macrophages and this effect was attributed to two amino acid-sesquiterpene conjugates (saussureamines A and B)\(^90\). *Saussurea lappa* was found to inhibit inducible nitric NO by decreasing iNOS protein and iNOS mRNA levels, through the inactivation of NF-kappaB, which contributes to the anti-inflammatory activities of *Saussurea lappa*\(^91,92\).

The active ingredients of *Picrorhiza kurroa* are iridoids (picroside I & II, 6-feruloyl catalpol and pikuroside)\(^93\). The ortho-methoxy-substituted catechol, apocynin, inhibits the release of superoxide anion (O2\(^*-\)) by enzyme DPH oxidase, by blocking the assembly of a functional NADPH oxidase complex\(^94\). Van den Worm showed that apocynin, isolated from *Picrorhiza kurroa*, selectively inhibits reactive oxygen species production by activated human neutrophils. A structure-activity relationship study showed that substances with an additional methoxy group at position C-5 display enhanced anti-inflammatory activity *in-vitro*\(^95\). Russo *et al.* also reported a dose-dependent free radical scavenging capacity, a protective effect on DNA cleavage and H2O2-induced cytotoxicity and DNA damage in human fibroblasts\(^96\). Baruah observed that *Picrorhiza kurroa* inhibited passive cutaneous anaphylaxis and protected mast cells degranulation\(^97\). Dorsch *et al.* identified the phenol glycoside androsin as the active compound that prevented allergen and platelet-activating factor induced bronchial obstruction\(^98\). Mechanism of mast cell anaphylaxis by *Picrorhiza kurroa* revealed inhibitory influence without affecting mast cell-IgE binding suggesting indirect effects of *Picrorhiza kurroa* through alteration of membrane structure and function\(^99\). In one study, pretreatment with *Picrorhiza kurroa* rendered animals less sensitive to histamine; and the bronchodilator effects of isoprenaline and adrenaline was markedly enhanced with less severe duration of the allergic bronchospasm. Furthermore, the total histamine content of the lung tissue was significantly less, and pretreatment was also found to exhibit inhibitory effect on the immunological release of histamine and SRS-A from chopped lungs\(^100\).

Sinha *et al.* observed selective, antigen specific augmentation of T-cell response by *Picrorhiza kurroa*\(^101\). Extract of *Picrorhiza kurroa* was found to stimulate cell-mediated and humoral immune responses and phagocytic function of the cells of the reticuloendothelial system\(^102\). Apocynin, a constituent of *Picrorhiza kurroa*, was shown to inhibit the formation of TXA2 leading to AA-induced aggregation of platelets and stimulated release of PGE2 and F2 alpha\(^103\). *Picrorhiza kurroa* also showed stimulation of nucleic acid and protein synthesis\(^104\). Phenols isolated from *Picrorhiza kurroa* have been shown to selectively inhibit the release of O2\(^*-\) by activated neutrophils, leaving the phagocytic capacity intact. Simons *et al.* reported the reaction of the phenols with secretory products from the activated neutrophils as a critical event, as the reaction products interfere with the assembly of a functional NADPH-oxidase in the membrane\(^105\). The complement activity inhibitory effect of *Picrorhiza kurroa* was proved as based on complement consumption rather than on chelation of Ca2+ and/or Mg2+ or on stabilization of the target cells in the complement assay\(^106\).

*Azadirachta indica* is effective against certain fungi, including *Trichophyton ruberum*, *Mentagrophytes*, *Trichophyton violaceum*, *Epidermophyton*, *Microsporum nanum*, *Trichosporon*, *Geotrichum*, *Epidermophyton floccosum* and *Candida*\(^107,108\). *Azadirachta indica* possesses a wide spectrum of antibacterial action against Gram-negative and Gram-positive microorganisms\(^109\) and it inhibits *Vibrio cholerae*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Mycobacterium pyogenes*, *Streptococcus mutans* and *Streptococcus faecalis*\(^110\). The potent antibacterial activity of *Azadirachta indica* is due to the inhibition of cell-membrane synthesis in the bacteria\(^110\). *Azadirachta indica* offers antiviral activity against
Vaccinia virus\textsuperscript{111}, Chikungunya, measles virus and group-B Coxsackie viruses\textsuperscript{112}. *Azadirachta indica* shows anti-inflammatory activity by suppressing microorganism-induced ROS and pro-inflammatory cytokines\textsuperscript{113}.

Karmakar et al.\textsuperscript{114} identified AlAI and AlAIIVb as two major allergenically active components present in *Azadirachta indica*, and immunoblot confirmed the IgE-binding activity of the proteins\textsuperscript{114}. Njiro et al. confirmed that *Azadirachta indica* enhances the immune response in vivo\textsuperscript{115}. *Azadirachta indica* increased IgM, IgG antibody titres (humoral immune responses) and enhanced macrophage migration inhibition (cell mediated immune responses)\textsuperscript{116}. *Azadirachta indica* selectively activates the cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge\textsuperscript{117}. *Azadirachta indica* inhibits the chemiluminescence generation by activated polymorphonuclear leukocytes\textsuperscript{118}. *Azadirachta indica* showed dose and time-dependent strong anticomplementary effects pronounced in the classical complement pathway assay\textsuperscript{119}. Azadirone 1, a limonoidal constituent of *Azadirachta indica* also found to possess potent cytotoxic activity against cancer cells\textsuperscript{120}.

Andrographolide, an active component isolated from *Andrographis paniculata*, prevents oxygen radical production, which inhibits NO production both in vitro and ex vivo\textsuperscript{121} and the antiradical activity proceeds by hydrogen abstraction from carbon C-15\textsuperscript{122}. Andrographolide suppresses the mitochondrial pathway of apoptosis via activation of the Akt-BAD pathway in HUVECs\textsuperscript{123}. Shen et al. reported that the prevention of ROS production through modulation of the PKC-dependent pathway confer andrographolide ability to down-regulate Mac-1 up-expression that is essential for neutrophil adhesion and transmigration\textsuperscript{124}. Another study indicated that andrographolide inhibits nitrite synthesis by suppressing expression of iNOS protein\textsuperscript{125}. Zhao et al. observed that *Andrographis paniculata* promoted PGI2 synthesis, inhibited TXA2 production, stimulated the synthesis of cAMP and impeded platelets aggregation\textsuperscript{126}. Puri et al. reported that andrographolides induced stimulation of antibody and delayed type hypersensitivity response, as measured by macrophage migration index and proliferation of lymphocytes\textsuperscript{127}.

*Andrographis paniculata* has significant antimicrobial activity against common pathogens due to the combined effect of the isolated arabinogalactan proteins and andrographolides\textsuperscript{128}. *Andrographis paniculata* also works on smooth muscle by blocking the voltage operated calcium channels inhibiting the Ca (+2) influx\textsuperscript{129}. Diterpenoids isolated from *Andrographis paniculata* have been reported to show potent cell differentiation-inducing activity towards leukemic cells\textsuperscript{130}. Andrographolide is quickly and almost completely absorbed into the blood following the oral administration, and is 55% bound to plasma proteins. Following oral administration of 20 mg, maximum plasma levels of 393 ng/ml were reached after 1.5-2 hours, half-life time was 6.6 hours, respectively. The calculated steady state plasma concentration of andrographolide for multiple doses after the normal therapeutic dose regimen, about 1 mg/kg/day) was 660 ng/ml, and the concentration in blood was 1342 ng/ml. It is intensely metabolized and renal excretion is not the main route for elimination\textsuperscript{131}.

Triterpenoid glucosides (Daucosterol, stigmasterol-3-O-glucoside and Ecliptasaponin C) are the active ingredients of *Eclipta alba*\textsuperscript{132}. Sawant et al. observed that *Eclipta alba* has potent analgesic\textsuperscript{133} and anti-inflammatory activities\textsuperscript{134}.

An arabinogalactan polysaccharide isolated from *Tinospora cordifolia*, showed protection against lipid peroxidation and this protective action has been explained by its high reactivity
towards diphenylpicryl-hydrazyl (DPPH), superoxide radicals and the hydroxyl radical. Goel et al. studied radioprotective antioxidant actions of *Tinospora cordifolia*. Prince et al. recorded a decrease in the plasma thiobarbituric acid reactive substances, ceruloplasmin along with an increase in the levels of glutathione and vitamin C by *Tinospora cordifolia*. Dhuley et al. observed reduction in chemotactic activity of macrophages, reduction in IL-1 production and inhibition of TNF by *Tinospora cordifolia*. Diwanay et al. recorded protection offered by *Tinospora cordifolia* against myelosuppression with an increase in white cell counts and antibody titers. *Tinospora cordifolia* causes a dose-dependent enhancement in cell-mediated immunity, as evident by macrophage activation. The anticomplementary and immunomodulatory activities of *Tinospora cordifolia* were hypothesized as due to inhibition of the C3-convertase of the classical complement pathway. Bishayi et al. reported that treatment with *Tinospora cordifolia* reversed chemically-induced immunosuppression, as evident by an increment in the functional capacities of macrophages. The activation of macrophages by *Tinospora cordifolia* leads to increase in GM-CSF, which leads to leucocytosis and improved neutrophil function. In a clinical study, Rege et al. observed normalization of phagocytic capacities of neutrophils in patients receiving *Tinospora cordifolia*. Arabinogalactan has been reported to have mitogenic activity against B-cells proliferation independent of macrophages. Singh et al. reported antitumor effect of *Tinospora cordifolia* by activating tumor associated macrophages.

The active ingredients of *Cassia fistula* are proanthocyanidin and flavonoids, which have potent antioxidant activity.

Therefore, in a nutshell the beneficial results offered by Purim tablets might be due to synergistic effects, i.e. anti-inflammatory, antioxidant, antimicrobial, antiallergic and immunostimulant activities of the polyherbal formulation with dependable safety from adverse events.

**CONCLUSION**

Atopic dermatitis is an expression of immunologic malfunction, which manifests as a spectrum of complicated clinical manifestations. This clinical trial observed highly significant rapid symptomatic relief and clinical improvement, with Purim tablets and there were no reported or observed adverse events. This study concludes that Purim tablets are clinically highly effective and safe in all types of chronic dermatitis.

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