Topical treatment of atopic dermatitis by silymarin

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ABSTRACT

Background: Atopic dermatitis is a chronic inflammatory disease that causes eczema, rashes, and itching. It is most common in younger people & adolescence. Recurrent relapses are a characteristic feature of atopic eczema. Anti-inflammatory therapy of exacerbations is aimed to control effectively disease activity and permit a return to basic dermatological therapy as soon as possible. Oxidative stress & inflammatory responses are thought to be responsible for the pathogenesis of atopic dermatitis. Silymarin is a polyphenolic flavonoid derived from the seed of milk thistle (*Silybum marianum* (L.) Gaertner) that has anti-inflammatory, antioxidant and cytoprotective effect. The aim of this study was to evaluate the anti-inflammatory effect of topical preparation of silymarin in atopic dermatitis.

Patients & method: Forty-three patients with atopic dermatitis (26 female, 14 male, 3 - 34 years old) were participated in the single blind, placebo controlled, 8-week trial. Of these, 10 patients were treated with 0.05 %, 10 patients were treated with 0.1 %, 10 patients were treated with 0.2 % topical preparation of silymarin, twice daily. The other 10 patients were received placebo twice daily.

Results: There was a statistically significant improvement. A statically significant was seen in mean total body surface area involvement over time. Mean total body surface area was 25.675% at baseline & decreased to 1% at 2-4 week.

Silymarin ointment was proven to act rapidly, to be highly effective, excellent improvements in pruritis, erythema, & skin irritation were noted in the patients who received 0.1 % & 0.2 % silymarin ointment topical treatment in comparison with the control group.

Conclusion: Topical treatment of silymarin is more effective, safe & may represent a breakthrough drug in the manegment of atopic dermatitis.

Keywords: Atopic Dermatitis, Silymarin. **(J Bagh Coll Dentistry 2005; 17(3):56- 61)**

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder. Like other allergic diseases, the prevalence of atopic dermatitis appears to be rising. In children, the prevalence of AD has increased from 3 -4% in the 1960's to 10-15% in the 1980's. But unlike many other diseases, AD has no primary skin lesions or pathognomenic test. Therefore, the diagnosis of atopic dermatitis has to be made by constellation of physical findings. The major features include pruritis, typical morphology and distribution of the lesions. The skin distribution varies with age.[1]

The histopathologic changes in atopic dermatitis are nonspecific. Acute lesions, characterized by intensely pruritic, erythematous papules, reveal mild epidermal hyperplasia, intercellular edema of the epidermis (spongiosis), and infiltration of lymphocytes and macrophages along the venous plexus in the dermis. In chronic AD, characterized by lichenification and fibrotic papules, there is increased hyperplasia and hyperkeratosis of the epidermis, and a persistent dermal inflammatory cell infiltrate with lymphocytes and macrophages, as well as increased mast cells and Langerhans cells.[2]

Many factors exacerbate AD.

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The atopic skin is associated with a lowered threshold of irritant responsiveness and pruritus.

Common triggers include: irritants, dry skin (xerosis), infections, allergens, sweating, changes in temperature, illness or fatigue, and emotional stress. Important irritants in atopic dermatitis are wool and acrylic in clothing, perfumes and perfumed products, cosmetics, soaps, cleaning agents, alcohol containing products, sand, tobacco smoke, paint, chlorine in swimming pools, and citrus foods.[3, 4]

The mechanism of how infections can exacerbate AD is becoming clearer by several studies on staphylococcus aureus. Over 90% of patients with AD are colonized with Staph aureus Recent studies suggest that Staph. Aureus can exacerbate or maintain skin inflammation in AD by secreting a group of toxins known to act as superantigens, which stimulate significant percentage of T cells and macrophages. Nearly half of AD patients produce IgE directed to staphylococcal toxins.[5]

Genetic factors are likely responsible for a variety of dermatologic and/or immunologic abnormalities which underlie AD. The immunologic abnormalities include hypersensitivity reactions, impaired immunoregulation of IgE, increased phosphodiesterase, impaired macrophage functions and increased mast cell releasability. With appropriate allergen stimulation, mast cells release mediators, which lead to itching.

Additionally, antigen stimulation causes T cells to differentiate into Th2 (T-helper2) cells and secrete cytokines leading to increased IgE and recruitment of eosinophils and other inflammatory cells. Elevated IgE and eosinophil products cause increased mast cell release of histamine and cytokines further potentiating the cycle of inflammation. The physical trauma of itching results in IL-1 and IL-3 secretion by keratinocytes; activation of Langerhans cells leading to secretion of IL-1, TNF-a, platelet activating factor and histamine releasing factor and additional activation of T cells, which further perpetuate the reaction.(6)

Moisturizers are the first line of topical therapy for AD, and are important to reduce and prevent the dry itchy skin of AD. Petroleum products such as Vaseline or hydrated petrolatum are the best moisturizers.(1) Tar preparations may act as antiprurutics, disinfectants, anti-inflammatory and desquamating agents when put in the bath or applied topically, and are often beneficial in both the acute and chronic phases of AD. Topical steroid ointments or creams are needed for acute flares of atopic dermatitis. Topical steroids should not be the sole treatment for atopic dermatitis, but should be used in conjunction with other forms of therapy.(7) Antihistamines may be helpful especially at night to control the itching associated with atopic dermatitis. Hydroxyzine or cetirizine and diphenhydramine are frequently prescribed.(8)

Herbs that may be helpful: the three categories of herbs used for people with eczema: anti-inflammatories and herbs that affect the immune system, immunomodulators, (Allium cepa, Calendula, Chamomile, Chickweed, licorice, onion) astringents (herbs that bind fluids and exudates)(Oak, Witch hazel), and herbs that affect the liver (also called alternatives)(Burdock, Red clover, Sarsaparilla, Wild oats). Alterative herbs are poorly researched. Astringents are only helpful if applied topically when weeping eczema is present; they will not help people with dry eczema.(9)

Silymarin is the name applied to a specific extract made from the seed of the milk thistle (*Silybum marianum* (L.) Gaertner), also known as St Mary's or variegated thistle. Like other thistles, it is a member of the daisy family, Asteraceae. (10) In modern times the use of milk thistle and silymarin has focussed on liver conditions. Weiss in 1988, paid it considerable attention in his famous work *Herbal Medicine* and recommends it for its hepatoprotective effect and as one of the best remedies for liver complaints such as hepatitis .(11) A monograph on milk thistle fruit was published by the German Commission E in 1986 in which the crude botanical drug (i.e. the fruit) is recommended for dyspeptic complaints, while silymarin is recommended for toxic liver damage and for supportive treatment in chronic inflammatory liver disease and hepatic cirrhosis.(12)

Silymarin is a standardized seed extract rich in a type of flavonoid compounds known as flavonolignans. The main flavonolignans in silymarin are the isomers silybin (also known as silibinin), silydianin, and silychristin. Silybin is formed by the oxidative combination of the flavonoid taxifolin with coniferyl alcohol. Silybin is regarded as the single most important constituent in silymarin and has been the subject of numerous biochemical and pharmacological studies. Other constituents identified in the silymarin extract include silybin oligomers, quercetin, taxifolin, and dehydrodiconiferyl alcohol.(13)

Absorption of the silymarin flavonolignans from the digestive tract is rapid but incomplete. Like many other phenolic compounds, silymarin appears to have low bioavailability in human. Peak plasma levels of silybin occur about 1.3 hours after oral administration, and the elimination half-life is about 6 hours. The main route of elimination seems to be with the bile, with urinary excretion playing a lesser role. Silybin and silychristin are excreted at least partly as glucuronides and sulfates in the bile. The high degree of liver specificity shown by silymarin may be due to enterohepatic circulation of the constituents, i.e. their excretion with the bile into the digestive tract from where they can be reabsorbed.(14)

The hepatoregenerative properties of silymarin appear to be due to the ability of silybin to accelerate the regeneration of hepatocytes following liver damage. Silybin stimulates protein synthesis and mitosis via activation of DNA-dependant RNA-polymerase-1. (15) According to the Commission E monograph on milk thistle, there are no known contraindications or side effects except for a mild laxative effect encountered occasionally with silymarin.(12) The acute toxicity of silymarin is very low, its subacute & chronic toxicity are

very low; the compound is also devoid of embryotoxic potential.[16] Milk thistle has an excellent safety profile. A substantial amount of evidence points to the lack of toxicity from its use.[17]

Recent studies suggest future use in dermatological & cosmetic products based on a number of activities including promoting healing at wound sites, improved burn healing & counteracting skin degeneration & ageing via anti-inflammatory and free radical scavenging mechanisms.[18]

The aim of this study is to evaluate the efficacy of anti-inflammatory effect of silymarin ointment compared to placebo and the improvement in skin severity in the treatment of atopic dermatitis.

MATERIALS AND METHODS

Subjects: There is no single clinical sign or a biological alteration, which is always detected, in atopic dermatitis. Therefore, the diagnosis of atopic dermatitis is based on the contemporary presence of some diagnostic criteria, the most well known of which were proposed by Hanifin and Rajka.[2]

Patients with moderate to sever atopic dermatitis were included in the study. Patients had definite atopic dermatitis diagnosed according to standard criteria. [2] Exclusion criteria included clinically significant cardiac disease, other serious intercurrent illness, active infection, pregnancy or lactation, & CNS or seizure disorder.

Materials: Silymarin was manufactured by Luna co. Germany, and was supplied as an ointment for topical use, at concentrations of 0.05%, 0.1%, and 0.2% white petrolatum used for preparation, SDI, Iraq.

Study design: Forty-three patients were treated for eight weeks with topical preparation of silymarin 0.05 %, 0.1 %, 0.2 %, twice daily. Forty patients had participated in (three patients do not complete the study), single blind, placebo controlled study.

Patients were monitored every 3 days for safety, efficacy, curing, and improvement. Assessments including total clinical severity score and total body surface area involvement. Total clinical severity score consisted of six parameters including: erythema, edema/papulation/induration, pruritus, excoriations/erosions, scaling/dryness and lichenification), each measured on a half-point incremental scale from 0 to 3 (1= mild, 2= moderate, and 3= sever).

Statistical analysis: Within–subjects repeated measures analysis of number & percentage of age group, treatment & improvement. Paired t-test were used to compare the results ($P< 0.05$). Chi-square analysis for improvement ($P < 0.05$). Pearson correlation (r) were used to assess the linear association between total body surface area involvement & total clinical severity score at baseline & change in these measures at the duration of the study.

RESULTS

In this study, there were 26 female, 14 male. The highest incidence was seen with 11-20 years & the high percentage was seen in females & it's statistically significant ($p< 0.05$, chi-square).

Figure 2 showed the percentage of silymarin concentration of male, female patients & control (0% placebo). The number of improvement with 0.1%, 0.2% is better than 0.05%, its dose dependent, as shown in figure 3. Figure 4 showed the duration of treatment by silymarin of patients and control. There was statistically significance between treatment & improvement ($P < 0.05$, Chi-square).

Efficacy was measured by evaluation of total body surface area & clinical scores. There was a statistically significant decrease in mean total body surface area involvement over time ($P < 0.05$, ANOVA). At baseline the mean total body surface area involvement was 25.7%. At 2-4 week mean total body surface area involvement had decreased to 1%.

Likewise, there was a statistically significant decrease in the clinical severity parameters. The mean total clinical severity score was 7.02 at baseline & decrease to 0.1 at 2-4 week ($P< 0.05$).

There was significant clinical improvement of skin lesions & also reduction in symptoms after topical treatment of AD by silymarin ointment. There was highly significant improvement with up to 95% reduction of the clinical score was recorded with all concentrations tested. The efficacy of silymarin would be comparable with placebo. The itching sensation was improved within 1-2 doses to 2 days.

DISCUSSION

Although the exact pathogenesis of atopic disease is unclear, Th2 cells play an important role. These cells elaborate cytokines, which recruit eosinophils to affected areas. Adhesion molecules may also be important. Their expression appears to be upregulated on endothelial cells of patients with atopic dermatitis. Adhesion molecules facilitate migration of leukocytes from the vascular compartment to surrounding tissues. The level of soluble adhesion factor in the circulation appears to correlate with expression on endothelial cells. Th2 cells appear to be central to the pathogenesis of atopic disease, and therefore anything that "suppresses" Th2 expression may help inhibit development of asthma, eczema, or allergic rhinitis.[19]

The local synthesis of allergen specific IgE in the skin result in mast cell cross- linking & activation & release of mediators; histamine, leukotrienes, & cytokines. Evidence for the involvement of these mediators include elevated plasma & tissue histamine, increase basophile release of histamine, increase cAMP specific phosphodiesterase & elevated levels of leukotriene B4 .[20, 21]

The transcription factor NF-kappaB is the central regulator for the expression of various genes involved in inflammation, infection and immune response including the genes for IL-1beta, TNF-alpha, and IL-6 and leukocyte adhesion molecules.[22] The method of action for milk thistle is not totally understood but it is thought to involve cell regeneration by stimulating protein synthesis and by up-regulating antioxidant and anti-inflammatory activity. Silymarin, the active component, has been shown to inhibit inflammatory agents NF-kappa B, TNF-alpha and leukotrienes.[23, 24] With the inhibition of inflammatory agents, the production of reactive oxygen intermediates and lipid peroxidation was correspondingly suppressed. This may explain the antioxidant properties of silymarin and why it's been shown to have protection against stage 1 tumor development. [23, 25, 26]

It has been hypothesized that silymarin may act by modulating the activation of regulating substances of the cellular cycle & of mitogen-activated protein kinase. Recent studies showed that silymarin inhibited TNF-induced activation of both NF-κB and apoptosis.[27] Other study found that silymarin blokes NF-κB dependent reporter gene expression. Several genes are involved, growth factors, cyclooxygenase-2, metalloproteases, & cell surface adhesion molecules.[28] The inhibitory effect of silymarin on NF-kappaB activation and cytokine release might be responsible for its anti-allergic effect as demonstrated in clinical studies. Silymarin has also been shown to have a potential positive effect on immune function by its ability to enhance neutrophil activity. Studies have shown that silymarin exert a number of effects, including inhibition of neutrophil migration, inhibition of kupffer cells, marked inhibition of leukotriene synthesis & formation of prostaglandins.[24,29] Silymarin can reduce formation of inflammatory eicosanoid by inhibiting the enzyme responsible for its formation (lipoxygenase), this explain other mechanism for the treatment of AD.[30] All previous mentioned studies explain the mechanism by which anti-inflammatory effect of silymarin in the treatment of AD.

Silymarin has ability to inhibit the enzyme 5-lipoxygenase and hence the formation of pro-inflammatory leukotrienes. A novel therapeutic approach in AD is leukotriene receptor antagonist [31], so silymarin is a novel drug for this approach, & this study confirms the above study.

The ability to stabilize cell membranes may explain the inhibition of histamine release from basophiles.[32] Silymarin has significantly reduced histamine output, this explain the relieve of strong itching, red puffiness, seen with eczema, by all concentrations used for topical treatment in this study.

Enzyme inhibitors of PLA2 and PDE 4 currently in the very early stages of clinical development also show potential promise as additional alternative strategies to topical treatment.[20] A number of skin abnormalities have been found in AD such as low cyclic AMP. The role of cAMP as a second messenger involved in the suppression of immune & inflammatory cell activity is well documented. Although agents that increase camp content inhibit the generation or release of a host of inflammatory mediators, considerable attention has focused on the regulation of inflammatory cytokines, particularly TNF-α. Elaboration of TNF-α from monocytes is strongly inhibited by prostacyclin analogs or phosphodiesterase inhibitors, agents that increase cAMP content. [33] Silymarin acts by this mechanism also, & confirm this study. Despite the rapid and proven

efficacy of topical silymarin ointment of different concentrations, no side effects can limit their clinical usefulness. Topical silymarin treatment is dose dependent

The author suggests using systemic treatment of silymarin for the treatment of AD, & using topical & systemic dosage form for the treatment of other skin diseases.

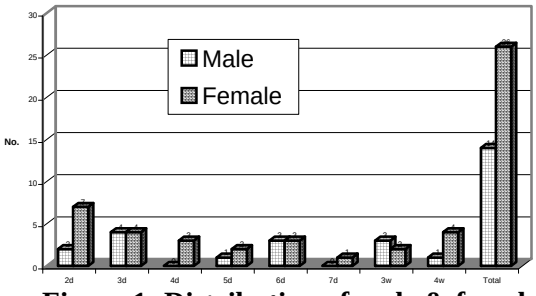

Figure 1: Distribution of male & female among age groups.

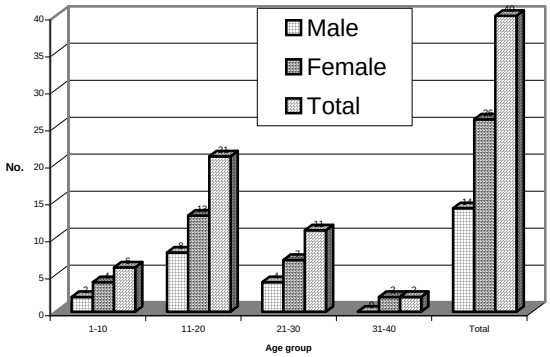

Figure 2: Percentage of silymarin concentration of male & female patients & control.

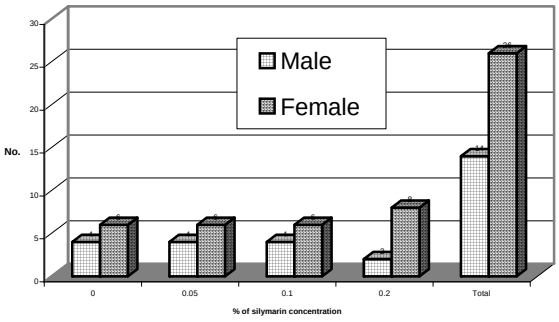

Figure 3: Number of improvement of treated patients & control (placebo).

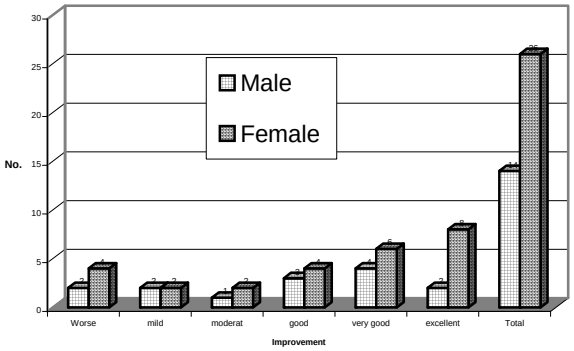

Figure 4: Duration of treatment by day of treated patients & control.

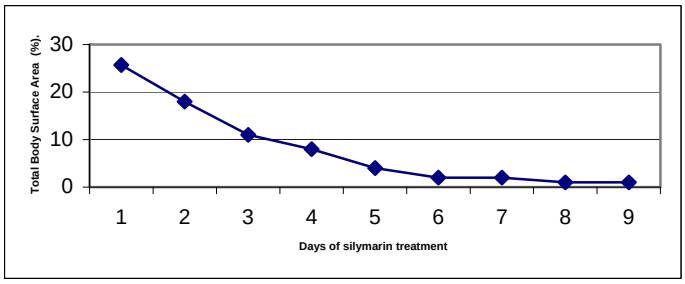

Figure 5: Reduction in total body surface area involvement over time (P < 0.05).

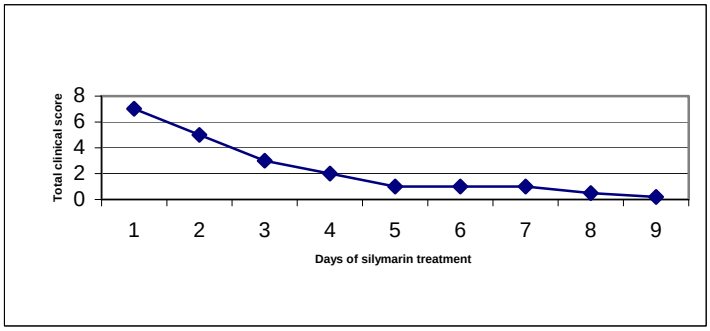

Figure 6: Reduction in total clinical score (P< 0.05).

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