

Bee venom and propolis as new treatment modality in patients with localized plaque psoriasis

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ABSTRACT

Psoriasis is a chronic skin disease with unsettled etiology. T-cells were suggested to be of major importance in its pathogenesis. Several therapeutic modalities have been used for treatment of psoriasis. Apitherapy entails the medical use of honey bee products as honey, bee venom and propolis. The objective of this study is to evaluate bee venom and propolis, as a new therapeutic modality for localized plaque psoriasis. Forty eight patients were randomized into four treatment groups: Group I received intradermal bee venom twice weekly; Group II received topical propolis ointment in vaseline base; Group III received oral propolis capsules 1 g/day; and group IV received intradermal bee venom, oral and topical propolis. Response to treatment was assessed by calculating Psoriasis Area and Severity Index (PASI) score and measuring serum interleukin-1 β (IL-1 β) before and after 3 months of treatment. A significant reduction in both PASI score and serum level of IL-1 β was observed in all groups. Changes in PASI score and IL-1 β were significantly higher in Groups I and IV compared to Groups II and III. All treatments were tolerable with minimal adverse effects. In conclusion, intradermal bee venom and oral propolis are safe and effective treatments of localized plaque psoriasis with minimal tolerable side effects. Intradermal bee venom has superior results than oral or topical propolis when used alone or in combination with propolis.

Key words: Bee venom, propolis, localized plaque psoriasis, serum interleukin-1 β .

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INTRODUCTION

Psoriasis is a common skin disease characterized by sharply demarcated chronic erythematous plaques covered by silvery white scales. The exact pathogenesis is not fully understood but is linked to activation of T-cells and several types of leucocytes that control cellular immunity through induction of different inflammatory cytokines and chemokines (Schön and Boehncke, 2005). Current treatments for psoriasis are only suppressive but not curative. The goal of treatment is to minimize the extent and severity of psoriasis to the point at which it is no longer disrupts substantially the patient's quality of life (Aschcroft and Wan, 2000).

Apitherapy is the medical use of various products of honey bee including raw honey (antioxidant properties

and preventive effects against disease of honey recently has been highlighted, Samarghandian et al., 2011), pollen (Kas'ianenko et al., 2011), royal jelly (have antitumor and antibacterial activity and a capacity to stimulate collagen production, Park et al., 2011), wax (Illnait et al., 2005), propolis (Ku et al. 1999; Chuu et al., 2012) and venom (Boyle et al., 2012). The therapeutic potential of apitherapy is still partially understood; however, the anecdotal evidence according to the American Apitherapy Society (Christopher, 1997) depicts its effectiveness in treating many diseases including rheumatic diseases (Liu et al., 2008), neurological diseases as multiple sclerosis (Wesselius et al., 2005; Mirshafiey, 2007; Bowling, 2010; Hegazi et al., 2010),

treatment of central post stroke pain (Yun and Sun, 2010) and dermatological conditions as eczema, psoriasis (Cherniack, 2010), cutaneous warts (Zedan et al., 2009) and herpes virus infection (Loyrish, 1961; Christopher, 1997).

Bee venom is secreted from venom gland in the late area of the worker bee. Its main components are: peptides as mellitin, apamin, mast cell degranulation peptide-401(MCD-peptide), enzymes as hyaluronidase, and non peptide components: as glucose, and fructose (Vanks and Shipolini, 1986). *Bee propolis* is a brownish resinous substance collected by bees and used to seal their hives. The main components of propolis are: flavinoids (that include quercetin, apegenin, galangin), phenolics (caffeic acid phenyl ester), and terpens (Burdock, 1998; Bankova et al., 1983; Hegazi and abd El Hady, 2002).

This investigation aimed at clinical and laboratory evaluation of bee venom and propolis, as a new treatment modality in patients with localized plaque psoriasis.

PATIENTS AND METHODS

Patients

Patients with systemic diseases, such as diabetes and cardiac diseases were excluded from the study. Pregnant and lactating females were also excluded. This study was conducted on 48 patients with localized plaque psoriasis affecting less than 30% of the skin, in the active stage of the disease (appearance of new lesions). They were collected from the Out-patient Clinic of Dermatology and Venereology Department, Tanta University Hospital, Egypt. All patients were asked to stop any topical or systemic treatment for at least one month prior to commencement of the study. The study was approved by the local ethical committee.

Clinical assessment

All patients were subjected to full history taking, thorough general and local clinical examination and routine laboratory investigations. Complete liver and renal function tests were done for all the patients before and after therapy. Psoriasis Area and Severity Index (PASI) score (Fredriksson and Pettersson, 1978) was calculated before and after treatment. Patients were also photographed at the first visit and at the end of therapy. Each patient signed a written consent form to be included in the study and to be photographed.

Treatment regimen

According to treatment received, patients were classified into 4 equal groups of 12 patients:

Group I

They received intradermal injection of bee venom. Bee venom was diluted in distilled water (Patent No. 8901/2006) and injected intradermal twice weekly starting with 0.01 μ l and then increased gradually by 0.01 μ l every other injection till reaching a dose of 1 μ l every injection (Won et al, 2000).

Group II

They received topical propolis (Egyptian propolis) in the form of ointment in vaseline base twice daily. The ointment was prepared as in Patent No. 8901/ 2006.

Group III

They received oral propolis (Egyptian propolis) in the form of capsules at a dose 1 g/day (Abdel Sabour and Hegazi, 2003) and in Patent No. 8901/ 2006.

Group IV

They received combined treatment of intradermal bee venom with oral and topical propolis (Egyptian propolis) as in Patent No. 8901/ 2006.

Treatment was given for the patients for 3 months with regular follow up every two weeks. Blood samples were taken from all patients before and after treatment to estimate serum IL-1 β levels using ELISA (Gruaz et al., 1989; Mizutani et al., 1991).

Evaluation of side effects

All the adverse events observed during the treatment period were recorded. To evaluate any possible systemic side effects of the treatment, the patients were subjected to complete blood picture, liver and kidney function tests at each visit, till the end of the treatment.

Statistical analysis

The patients in this investigation were collected at random. Statistical analysis of the present study was done, using the SPSS version 12. For quantitative data, the mean and standard deviation were calculated. The differences between means were statistically analyzed using ANOVA test and Chi-square tests as Senedcor (1961).

RESULTS

The study included 48 patients with localized plaque psoriasis. They included 26 males and 22 females. Their ages ranged from 8 to 60 years with a mean of 35.91 ± 11.89 years. The duration of psoriatic lesions ranged from 4 months to 7 years with a mean of 2.34 ± 0.56 years. Patients with systemic diseases, such as diabetes and cardiac diseases were excluded from the study. Pregnant and lactating females were also excluded.

Treatment efficacy

All groups of patients showed reduction the mean PASI score after the end of treatment. In Group I, the mean PASI score of the patients was 6.67 ± 0.83 before treatment and was reduced after treatment to a mean of 3.17 ± 0.41 . The reduction was statistically highly significant ($P < 0.01$), (Figures 1, 3a and b). Similarly,

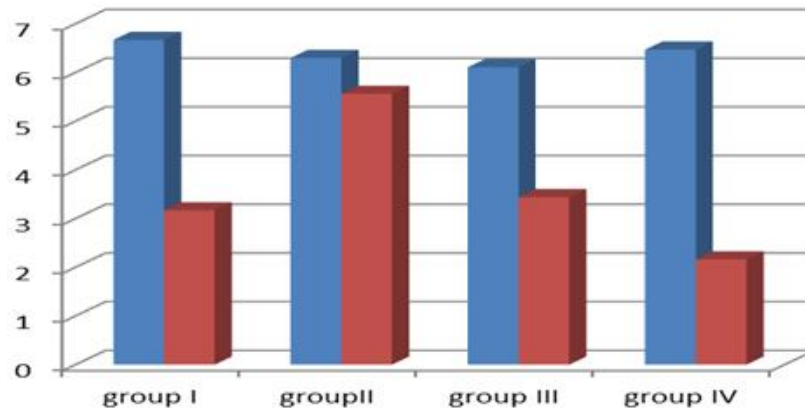


Figure 1. PASI score before and after treatment in all groups.

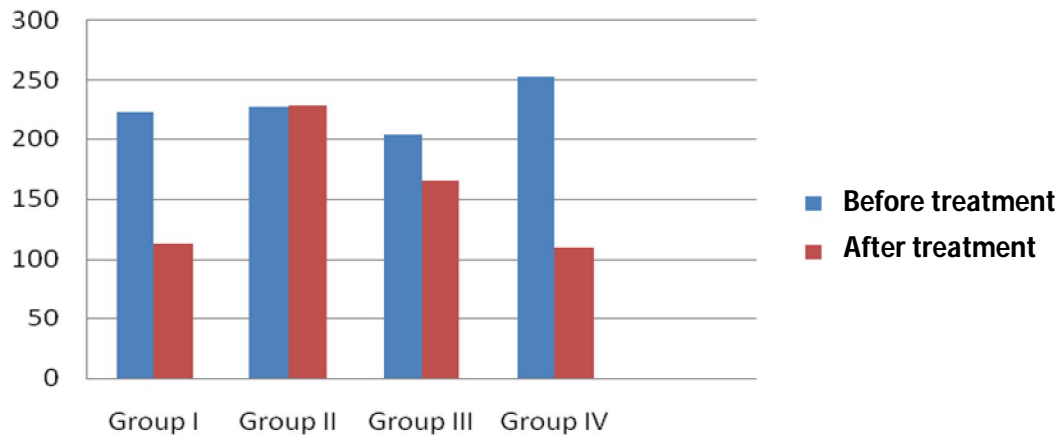


Figure 2. IL-1 β before and after treatment in all groups.

Group IV showed a statistically highly significant reduction the mean PASI score from 6.47 ± 0.96 to 2.16 ± 0.02 ($P < 0.01$), (Figures 1, 6a and b).

However, in Group II, the mean PASI score of patients was 6.30 ± 0.08 before treatment and was reduced to 5.56 ± 0.40 after treatment. This reduction was statistically insignificant ($P > 0.05$), (Figures 1, 4a and b). In group III, the mean PASI score was reduced from 6.11 ± 0.64 before treatment to 3.44 ± 0.29 after treatment. The difference was statistically significant ($P < 0.01$), (Figure 1, 5a and b). The mean percentage change in PASI score was highest in group IV (75 ± 0.21) followed by Group II (67 ± 0.27), then Group I (57 ± 0.23), while Group III showed the lowest mean percentage reduction in PASI score (47 ± 0.40). In all groups, patients started to show improvement after 4 weeks and the 1st sign of improvement was the decrease in scaling, then erythema, and then infiltration.

Serum level of IL-1 β was measured for all patients before and after treatment. In Group I, the mean level of IL-1 β was 222 ± 4.13 before treatment and reduced to

113 ± 3.73 after treatment with a statistically significant difference ($P < 0.05$). Similarly, in Group III, the mean IL-1 β level was 203 ± 3.41 before treatment. After treatment, it was reduced to 165 ± 4.33 ; this reduction was statistically significant ($P < 0.01$). Group IV showed a statistically highly significant reduction in the mean of IL-1 β level from 252 ± 1.05 before treatment to 110 ± 3.18 after treatment ($P < 0.01$) (Figure 2). In Group II, the mean level of IL-1 β was 227.7 ± 1.06 before treatment and 228.6 ± 5.21 after treatment with no statistically significant difference ($P > 0.05$) (Figure 2). The mean percentage change in IL-1 β was highest in group IV (60 ± 0.11) followed by Group I (52 ± 0.24), then Group III (18 ± 0.78), while Group II showed the lowest mean percentage reduction in IL-1 β (0.67 ± 0.05).

Side effects

During the study, 2 patients in Group III discontinued treatment and one patient in Group II showed worsening

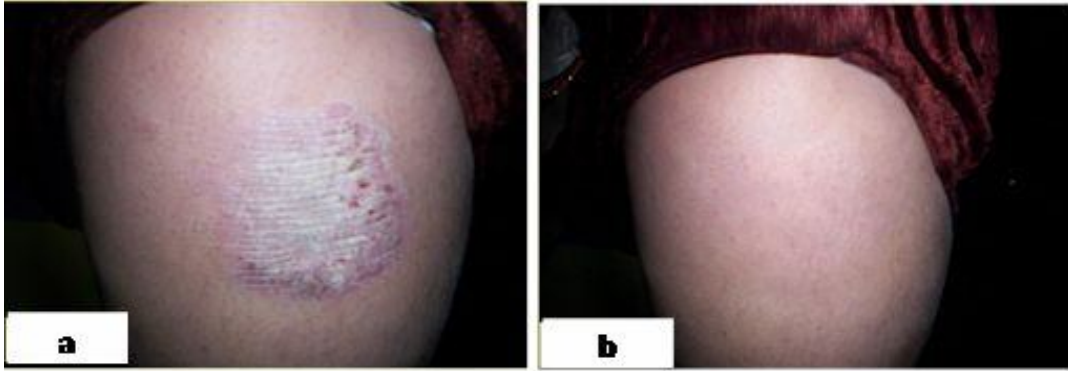


Figure 3. (a) Patient in group I before treatment; (b) the same patient after treatment.

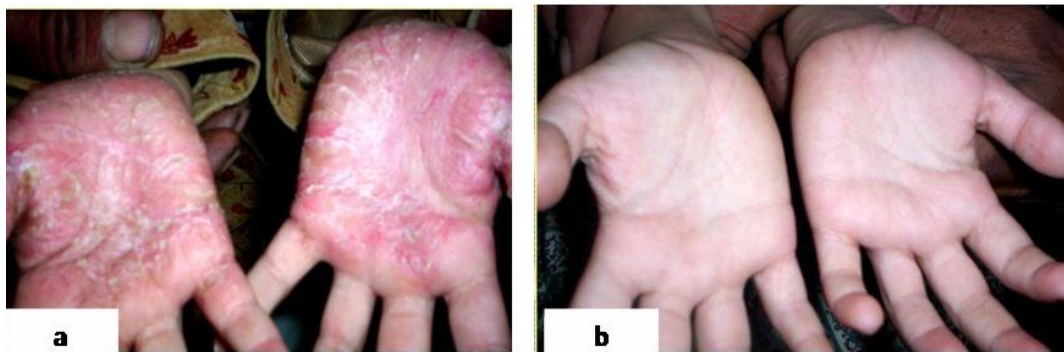


Figure 5. (a) Patient in group IIB before treatment; (b) The same patient after treatment.

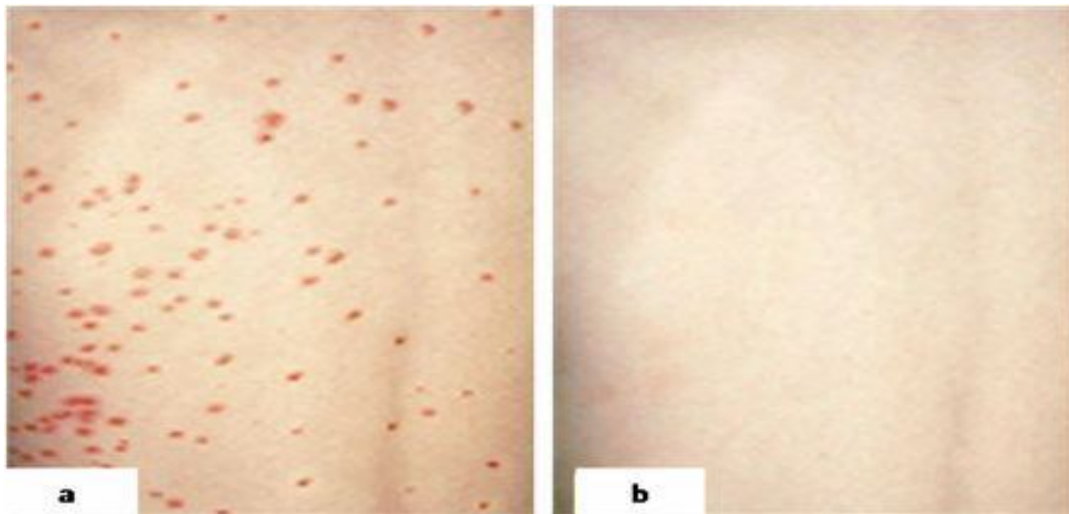


Figure 6. (a) Patient in group III before treatment; (b) The same patient after treatment.

of the psoriatic lesions with increase in PASI score. Moreover, 2 patients including one patient in Group II and the other patient in Group III showed no clinical evidence of improvement with any change in their PASI score after completion of the course of treatment. During the course

of therapy, 4 patients in Group I and 2 patients in Group IV experienced generalized itching; however, it was not so significant to necessitate discontinuation of therapy. Itching was completely resolved spontaneously within few weeks.

There were no systemic side effects of treatment in all patients as detected by routine investigations and follow up.

DISCUSSION

Clinical and laboratory evaluation of the use of bee venom and propolis as new treatments in localized plaque psoriasis was studied. In this study, there was overall reduction in the mean PASI score and the mean IL-1 β levels after treatment. This may reflect the possible therapeutic effect of both bee venom and propolis in treatment of localized plaque psoriasis. Patients, in Groups I and IV, who received bee venom (either alone or in combination with propolis) showed more significant reduction in their mean PASI score than patients who received propolis alone. This finding may indicate that bee venom is more effective than propolis in treatment of psoriasis.

To the best of our knowledge, this is the first study to evaluate the clinical effect of treatment with bee venom and propolis in patients with psoriasis. El-Banby (1987) previously suggested that bee venom could be used in treatment of psoriasis.

In the current study, apart from Group II, the mean level of IL-1 β was significantly reduced after treatment in all treatment groups. These results were in accordance with Mizutani et al. (1997), who reported a reduction in the level of IL-1 β in patients with guttate psoriasis from 289.5 ± 56.1 to 29.2 ± 4.9 after clinical improvement of psoriasis following tonsillectomy operation. They suggested that inflammatory cytokines IL-1 β , TNF- α and IL-6 from monocytes are involved in the pathogenesis of psoriasis and reduction in their levels occurs with clinical improvement of the disease. The non-significant reduction in IL-1 β in Group II, who received topical propolis only, might be because propolis acted locally with minimal systemic effect.

To our knowledge, this is the first report on changes in the level of IL-1 β in psoriasis patients treated with bee venom and propolis. However, reduction in the level of IL-1 β was also reported in the treatment of other non-dermatological diseases using bee venom. Nam et al. (2003) reported a reduction in the IL-1 β level following successful treatment of different types of arthritis with bee venom. They suggested that the pharmacological effect of bee venom in arthritis may be due to the blocking effect on pro-inflammatory cytokines as TNF- α and IL-1 β production.

In this work, Group IV showed the highest reduction in the mean PASI score and IL-1 β level among other groups. This marked reduction in PASI score and IL-1 β could be attributed to the synergistic effect of action of both propolis and bee venom which were used in combination in this group of patients.

The exact mechanism of action bee venom and propolis

in treatment of psoriasis is still not settled. However, bee venom may exert its action through the effect of its components. Melittin has the ability to block the expression of inflammatory genes. So, it effectively reduces inflammation by inhibiting the critical DNA binding activity of NF- κ B (Nuclear Factor Kappa B), which directly controls a number of genes involved in immune reactions (Park et al., 2004). The pharmacological activities of bee venom on the inflammatory process could be also through inhibition of Cox-2 expression that is involved in the production of prostaglandins (PG) which supports the inflammatory process (Nam et al., 2003). Moreover, bee venom may act through reduction of IL-6 that increases in psoriasis (Kwon et al., 2002) and induction of IL-10 (Magnan et al., 2001) that causes improvement of psoriasis, and is used as a new line of psoriasis therapy (Friedrich et al., 2002).

Propolis may exert its effect in psoriasis through different mechanisms. It was shown that different propolis extracts as flavonoids and caffeic acid phenyl ester (CAPE) play an important role on human immune cell functions. Using propolis, cytokines produced by monocytes / macrophages (IL-1 β and IL-12) and by Th1 type (IL-2) lymphocytes were found to be suppressed, whereas the production of TGF- β 1 by T regulatory cells was ascertained to be increased. These data might indicate that propolis has a direct regulatory effect on basic functional properties of immune cells (Ansorge et al., 2003). Korytko and Boje (1996) observed that propolis extracts inhibit nitric oxide (NO) production by lipopolysaccharide (LPS)- stimulated macrophages. Furthermore, caffeic acid phenethyl ester (CAPE), one of the propolis components, inhibits lipoxygenase pathway of arachidonic acid, resulting in anti-inflammatory activity (Mirzoeva and Calde, 1996). Also, quercetin, another component of propolis has a significant anti-inflammatory activity due to direct inhibition of several processes of inflammation via interaction with calcium channels and/or calmodulin, as well as through other mechanisms such as by inhibiting mast cell and basophil degranulation, neutrophil and monocyte lysosomal secretion, prostaglandins (PG), leukotriene formation and lipid peroxidation (Hegazi and Abd El Hady, 2002; Abd El Hady et al., 2007) resulting in inhibition of release and manufacture of histamine and inflammatory mediators (Mirzoeva and Calde, 1996; Burdock, 1998).

Four patients in Group I and 2 patients in Group IV experienced generalized itching that improved on continuation of treatment. Occurrence of itching during treatment with bee venom was reported also by Lima and Brochetto-Baraga (2003), who explained it by presence of melittin and MCD- Peptide that cause degranulation of mast cells and release of histamine. On the contrary, Magnan et al. (2001) reported that bee venom immunotherapy induces IL-10 that causes suppression of allergic inflammation.

Interestingly, unlike most treatments used in psoriasis,

no systemic side effects were detected in all patients included in the study. This may indicate that this new treatment is a safe modality of treatment and could be used in patients with impaired liver or renal functions. However further studies on larger scale of patients and longer follow up periods are needed to confirm these results.

Conclusions

From the study, we conclude that intradermal bee venom and oral propolis could be a potential new therapeutic agent in treatment of chronic localized plaque psoriasis, with minimal tolerable side effects. Intradermal bee venom has superior results than oral or topical propolis when used alone or in combination with propolis. Interleukin-1 β could be considered as an indicator in treatment of psoriasis with intradermal bee venom. Larger randomized controlled complementary studies are needed to explore their efficacy. This work is a potential starting point for larger studies with wider scales of applications to confirm our findings.

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