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Clinical evaluation of AKBBA in the management of psoriasis

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Summary

***Introduction*. Psoriasis is a common chronic inflammatory, immune-mediated disease that predominantly affects the skin and joints, characterized by circumscribed, red, thickened plaques with an overlying silver-white scale (1). Though many pharmaceutical drugs and biologics are available in the market, they have very less impact on the psoriatic patients due to their own and many limitations. Therefore, as a complementary and alternative medicine (CAM), *Boswellia serrata Roxb* has been explored and found to be safe and efficient in the management of mild to moderate psoriasis.**
***Objective*. In the current study, we aimed at investigating a cream of *Boswellia serrata Roxb* extract standardized for 5% of 95% 3-O-Acetyl-11-Keto Beta Boswellic Acid (AKBBA) (in the form of a cream), for the management of mild to moderate chronic plaque Psoriasis.**
***Method*. An open label, multi centred phase III clinical trial, evaluating 200 psoriatic patients with application of AKBBA cream thrice a day for a period of 12 weeks was carried out. Changes in 'modified' Psoriasis Activity Severity Index (PASI) & biomarkers (LTB4, TNF alpha, VEGF, PGE2) from the baseline values along with remissions in clinical lesions observed through photographic images were considered for efficacy evaluation.**
***Results*. Highly significant changes in LTB4 ($p<0.001$) & TNF alpha ($p<0.01$) values from the baseline along with significant changes ($p<0.05$) in VEGF & PGE2 were observed. Reduction in 'modified' PASI score from the baseline visit was in consensus with the global evaluations by physician and patients.**
***Conclusion*. We propose topical application of AKBBA cream, may be useful in the management of mild to moderate chronic plaque psoriasis.**

KEY WORDS: Boswellia serrata; psoriasis; leukotrienes; boswellic acids; AKBBA.

Introduction

Epidemiological studies from around the world have estimated the prevalence of psoriasis to be in the range of 0.6 to 4.8% (2). Discovery of safer and more effective anti-psoriatic drugs remains an area of active research at the present time (3). It has recently been suggested that innate immune responses driven by neutrophils, macrophages or keratinocytes play an important role in the pathogenesis of psoriasis (Bos et al., 2005). Early and active psoriatic lesions are characterized by intra-epidermal penetration of activated polymorphonuclear leukocytes, which cause uncontrolled production of reactive oxygen species (ROS), leading to peroxidative damage to membranes of the skin and contributing to the exacerbation of lesions (Briganti and Picardo, 2003; Yildirim et al., 2003; Okayama, 2005). ROS may also activate phospholipase A2 (PLA2) and thus increase the release of mediators of arachidonic acid (AA) (Yildirim et al., 2003). Psoriatic patients present elevated levels of leukotriene B4 (LTB4) (Ikai, 1999), a potent chemoattractant molecule formed by 5-lipoxygenase (5-LO)-dependent metabolism.
A correlation of our earlier *in vitro* and *in vivo* studies using Boswellic acid reveals a decline in plasma concentrations of Tumour necrosis factor-α (TNF-α), Vascular endothelial growth factor (VEGF), Prostaglandin E2 (PGE2) and Leukotriene (LTB4) values, suggesting their role in the management of chronic inflammatory conditions. With encouraging results from the preliminary study, the present study was undertaken to evaluate the safety and efficacy of AKBBA in patients suffering from mild to moderate chronic plaque psoriasis.

Methods

An open label multicentre study was designed to evaluate the safety and efficacy of 5% of 95% 3-O-Acetyl-11-Keto Beta Boswellic Acid (AKBBA), in the form of cream for the management of psoriasis. The study was conducted at 8 centres across India, between Jan 2007 and Oct 2007. All the respective Institutional Ethics Committee approvals were obtained for the conduct of this study. The study details were provided to all the subjects and a written Informed Consent was obtained prior to study screening procedures. Out of 239 adult patients with mild to moderate chronic plaque psoriasis screened and enrolled across 8 clinical sites/hospitals in India, 25 were screen failures and 14 drop outs citing various personal reasons. Data of 200 subjects who completed the entire study duration of 12 weeks was considered for statistical analysis and further interpretations. The study was conducted in accordance with the ethical principles that have their origin in Declaration of Helsinki (World Medical Association) and in strict adherence to the clinical study protocol.

Inclusion and exclusion criteria (Figure 1)

Only patients aged over 18 years and less than 65 years of age, with mild to moderate psoriasis were included. Patients who had more than 50% of body surface area covered by psoriasis lesions were excluded, using 'modified' PASI (Psoriasis Activity and Severity Index) scoring system. Patients on anti-coagulant therapy, using non-immunosuppressive medication within past two months, presence of other skin lesions like actinic keratoses or lentigo or photo damaged skin were not considered for this study. Those patients who had used systemic or intralesional therapy or photo (chemo) therapy for psoriasis in the previous month were excluded. Also individuals with concomitant bacterial, fungal, or viral skin infections, pregnant or sexually active women who do not use contraceptives, non compliant patients were excluded with appropriate counselling. Patients with history of renal, hepatobiliary, or malignant disease, hypertension or recurrent acute infections, or any other evidence of severe illness or any other conditions that would make the patients, in the opinion of the investigator, unsuitable for the study were not considered.

Duration and study procedures

This trial was conducted over a period of 12 weeks. At the baseline (week 0) or screening visit, a complete physical and clinical examination was done for all subjects. Photographs of the clinical lesions were captured. Laboratory tests including (Complete Blood Chemistry) CBC, Liver Function Tests, and Renal Function Tests were performed. Subjects were advised to visit the clinical site/hospital at week 3, week 6, week 9 and at week 12. Physical & clinical examinations were performed on all the visits and blood samples were collected on week 12 for laboratory testing.

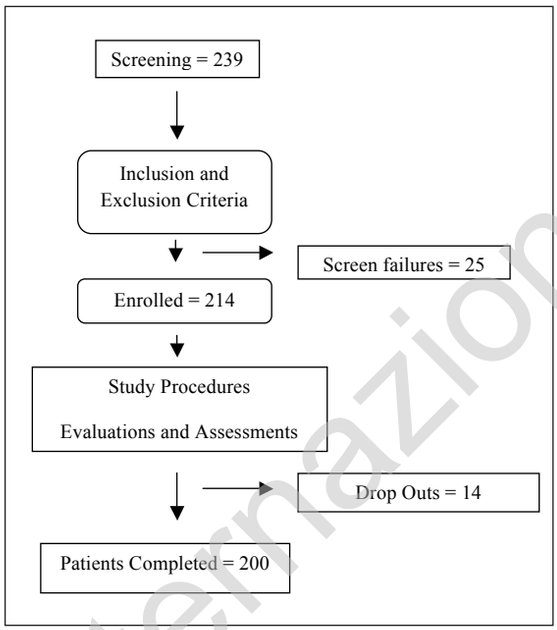


Figure 1 - Out of 239 patients screened for the eligibility criteria, 25 were found to be screen failures and all the 214 enrolled patients underwent study procedures. During the course of the study, 14 opted out citing various personal reasons, 200 patients completed the study and for whom all the study evaluations and assessments were accomplished.

Dose and dosage regimen

Boswellia serrata extract in the form of a cream standardized for 5% of 95% 3-O-Acetyl-11-Keto Beta Boswellic Acid (AKBBA) was dispensed to all the subjects on baseline visit, week 3, week 6 and week 9 visits with quantum sufficient and was advised to apply it topically to the affected area three times a day for 12 weeks.

Efficacy evaluations (Figures 2, 3, 4)

Biomarker evaluations (Table 1). Above and beyond these general tests, specific biomarkers like TNF alpha, VEGF, PGE2 and LTB4 were also evaluated. Clinical symptoms and signs were assessed and captured in the pre designed case report forms.

Estimation of serum biomarkers. ELISA kits (Invitrogen Corporation, CA) were procured from Life Technologies, Mumbai. Serum biomarkers like TNF –alpha, VEGF, PGE2, LTB4 were quantified by following a standardized protocol of Invitrogen. Besides clinical symptoms, subjects whose serum biomarker values were greater than the normal ranges, as defined in the protocol, were considered for inclusion on the baseline or screening visit.

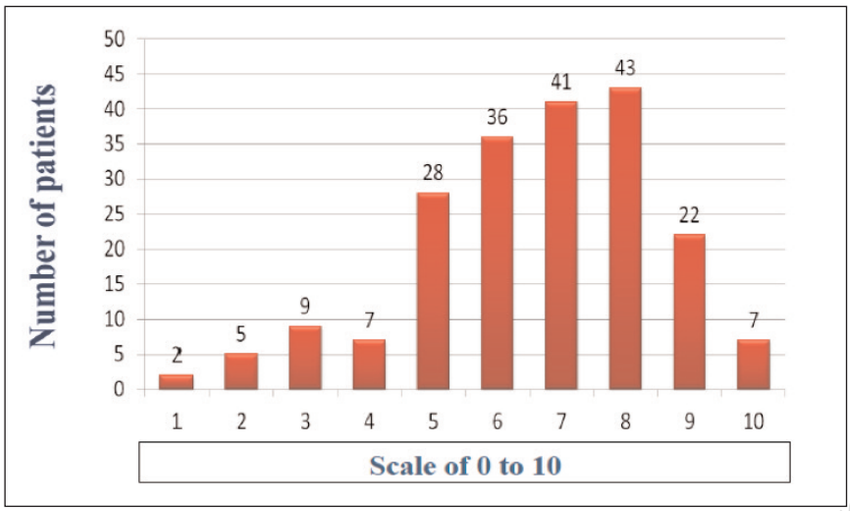


Figure 2 - "Global evaluation by the Physicians", improvement of symptons on a scale of 0 to 10 on the last study visit.

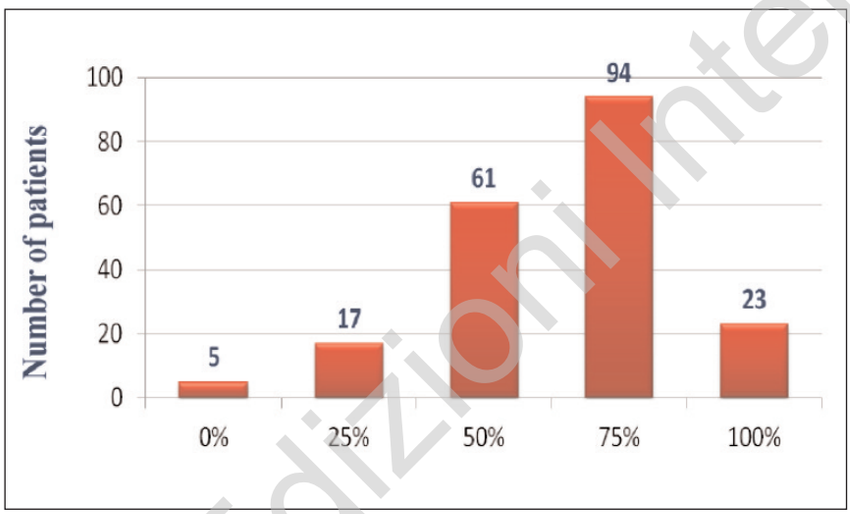


Figure 3 - "Global evaluation by patients", percentage improvement in symptoms from baseline to last visit.

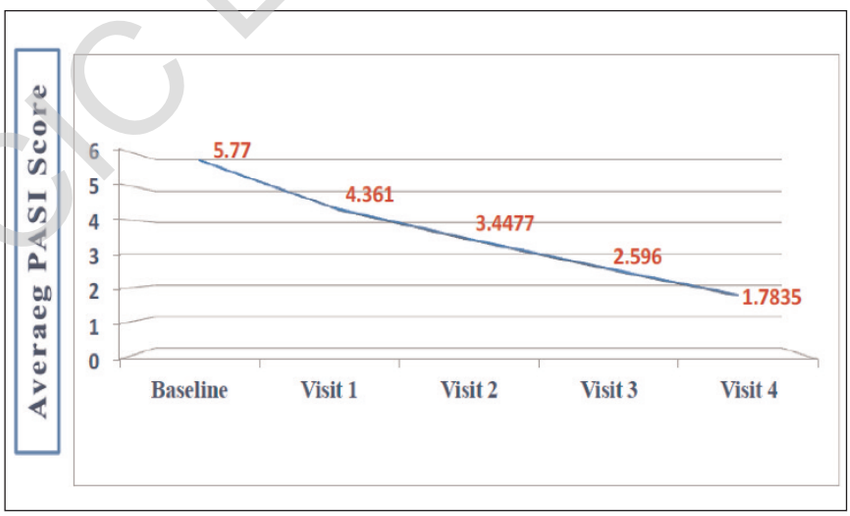


Figure 4 - Subjects' Mean 'modified' PASI (Psoriasis Activity and Severity Index) Scores at Various Visits.

Table 1 - Changes in serum biomarkers from baseline visit to final visit.

Biomarker	Mean baseline value (pg/mL)	Mean final value (pg/mL)	% reduction from Baseline	Normal Range (pg/mL)
TNF alpha	6.02 ± 0.29	2.51 ± 0.14**	58.3	2.5 ± 1.5
VEGF	143.88 ± 8.36	97.99 ± 5.19*	31.9	50 ± 15
PGE2	975.28 ± 19.44	634.58 ± 23.02*	34.93	525 ± 150
LTB4	510.92 ± 26.13	179.5 ± 8.82***	64.87	200 ± 100

*Values are mean ± SE, * p<0.05, **p<0.01, ***p<0.001*

Table 2 - Changes in "modified" PASI score from baseline visit to final visit.

Visit	Baseline	Visit 1*	Visit 2*	Visit 3*	Visit 4*
PASI score	5.8 ± 0.27	4.36 ± 0.22	3.48 ± 0.17	2.60 ± 0.14	1.78 ± 0.13

*Vales are mean ± SE, *significant at p<0.05*

Global evaluations by physicians. Global evaluation was carried out by the Physicians on the last visit of the study and the improvement was rated on a scale of 1 to 10, with 1 representing Bad and 10 standing for Good. This evaluation was done as a response to the question "How much better do you feel?"

Global evaluations by patients. Similarly, at the end of the study patients were also asked to assess the improvement in their symptoms as a percentage improvement from baseline, ranging from 0%, 25%, 50%, 75% and 100%.

The first, second, third and fourth visits were carried out at week 3, week 6, week 9 and week 12 respectively from the baseline (i.e., week 0 visit). At these visits, complete physical examination, concomitant therapy, clinical examination and assessment of the adverse effects for the enrolled subjects were performed. Additionally, all the diagnostic tests and clinical photographs were carried out on the baseline and last visit.

PASI score (Table 2) ***and photographs*** (Figure 5). The 'modified' PASI scoring system was used to clinically assess psoriasis over time and to monitor the response to therapy. Following are the elements of PASI system that were considered:

(1) Body regions as percent of body surface area
(2) Extent of body region affected
(3) Extent of psoriatic changes.

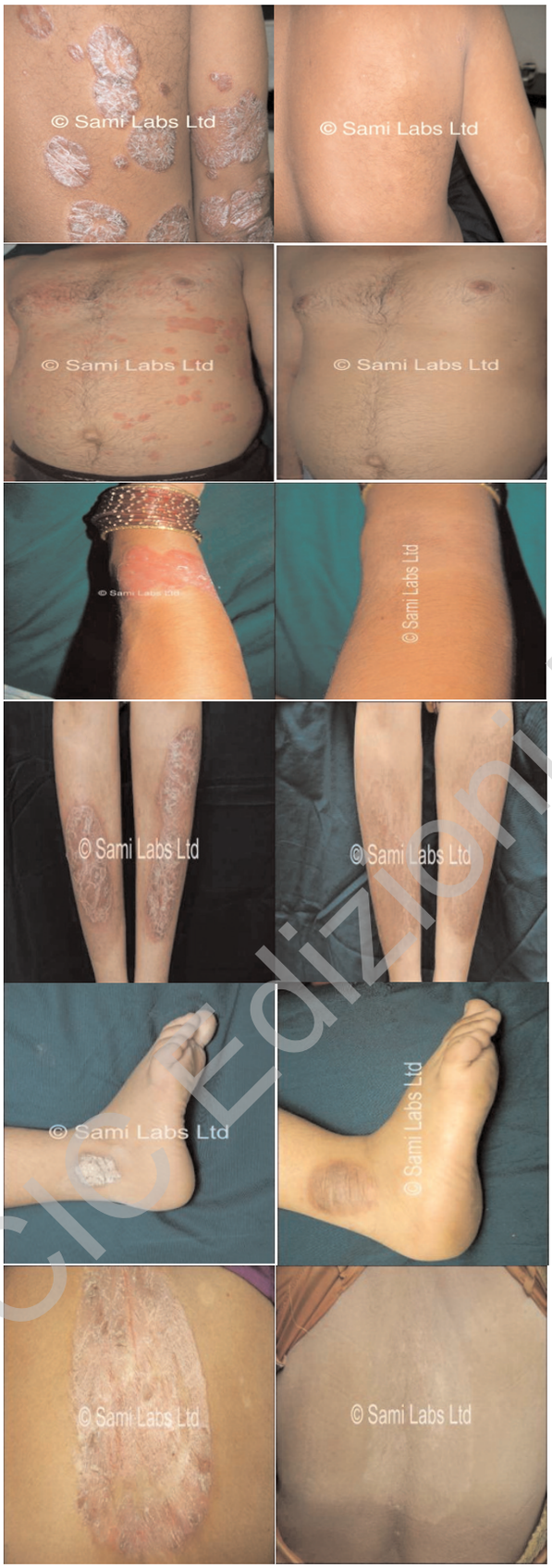
Figure 4 indicates the reduction of mean 'modified' PASI score ranging from 75 to 50% and was considered as an indicator of efficacy of the drug under test.

Results

Data of 200 completed study subjects/patients in mean ± SE for various parameters has been considered for interpretations. Student's paired t test was applied to the serum biomarkers and 'modified' PASI scores data. All the tests were two tailed and p<0.05 was considered statistically significant. Whereas, for Global evaluation by physician and by patients, percentage (%) reduction of scores from the baseline visit to final visit was used for analysis and interpretations. In the safety parameters, no significant change was demonstrated in the haematological, liver function and renal function laboratory tests, from baseline to the final visit values. Across 8 clinical centres, 13 adverse events have been reported to the respective sites with majority being contact dermatitis which was moderate in severity; three of them were categorized as unlikely due to study drug, three as possibly due to study drug, five as probably due to study drug and remaining two were considered as unrelated to study drug.

Discussion

The gum exudates from *Boswellia serrata Roxb* has been used in traditional medicine for treatment of inflammatory disease since antiquity. It is a moderate deciduous tree which is found in abundance in the dry hilly parts of India, Northern Africa and the Middle East. It is commonly known as Frankincense, Gajyabhakshya or Dhup. Compelling evidences indicate that the production of TNF alpha plays a central role in psoriasis by sustaining the inflammatory process in the skin as well as the joints (4). The decrease of TNF- alpha and VEGF, are already implicated in the pathogenesis and clinical activity of the disease (5). In another study, a statistically significant direct correlation was found between the PASI score and the lesional amounts of TNF alpha (6). TNF α activated skin macrophages led to Psoriasis like skin inflammation while treated skin showed reduced levels of inflammation and TNF alpha (7). In the present study TNF α showed a reduction of 58.3% from baseline in 12 weeks i.e. the abnormally



Figures 5 - In the left column samples of “before treatment”, and in right column the respective samples of “after treatment”.

raised values due to the inflammatory process were brought down to the normal range and is significant at p<0.01.

Angiogenesis appears to be a first order event in both psoriasis and related arthritis (8). Among the angiogenic factors, the cytokine VEGF plays a central role in the initiation of angiogenesis. It is the only mitogen to specifically act on endothelial cells and stimulate the elongation, network formation, and branching of non-proliferating endothelial cells in cultures deprived of oxygen and nutrients. High levels of VEGF have been found in the synovial joints of Psoriatic arthritis (9), and psoriatic plaques (10). A correlation has been seen between the PASI score and VEGF (11). Thus reduction in VEGF represents a step down in the inflammatory process involved in psoriasis. VEGF showed significant (p<0.05) reduction of 31.9% from baseline in the 12 weeks of the study. Although the final value did not come in the normal range, the reduction was quite remarkable.

Arachidonic acid and its metabolite levels are always raised in the psoriatic skin. The transformation of PGE2 into PGE2 alpha has been enhanced in the skin specimen from psoriatic plaques (12). Levels of both these prostaglandins have been seen to be raised in psoriasis (13, 14). Thus levels of PGE2 as arachidonic acid metabolites are good markers for evaluating the state of inflammation in psoriasis. In this study PGE2 not only demonstrated a significant (p<0.05) decrease of 34.93% reduction from baseline but also its values returned to normal range from the abnormally high values observed at the start of the study.

Leukotrienes are biologically active 5-lipoxygenase products of arachidonic acid metabolism that are involved in the mediation of inflammatory disorders. Leukotriene B4 is by itself a potent chemo attractant for Neutrophils. Neutrophils play an important role in psoriasis pathology (15). Higher levels of LTB4 are found in both acute and chronic skin lesions than in the normal skin. Also when applied topically to normal as well as the uninvolved skin of psoriatic patients, it induced features of psoriasis like edema and formation of intra dermal neutrophilic micro-abscesses (16-20). It may even be an important mediator in pain in inflammation (21). Thus LTB4 is not only a good representative as an arachidonic acid metabolite but also a biomarker for the inflammatory status.

In this case LTB4 exhibited a reduction of 64.87% from baseline. Its values were highly significant (p<0.001) from the earlier pathologically high values seen at baseline, exhibiting the generalized reduction in inflammation.

Patients suffering from psoriasis were found to have elevated plasma concentrations of Tumour necrosis factor-alpha (TNF-alpha), Vascular endothelial growth factor (VEGF), Prostaglandin E2 (PGE2) and Leukotriene B4 (LTB4) which was confirmed on the baseline visit; with the product under study, there was a statistically significant reduction in plasma concentrations of TNF-alpha, VEGF, PGE2 and LTB4.

Boswellia serrata extract have been scientifically tested in diseases like Osteoarthritis (22), Bronchial Asthma (23), Crohn's Disease (24), inflammatory bowel disease (25), and Intracranial Peritumoral edema (26-28). Recent studies have shown that only four β-Boswellic acids are effective anti inflammatory components (29).

Boswellic acids have an anti-inflammatory action like the non steroidal anti inflammatory drugs (NSAIDS). But as compared to NSAIDS, boswellic acids do not cause reduction in the glycosaminoglycans (30). *Boswellia serrata* extract standardized for 5% of 95% 3-O-Acetyl-11-Keto Beta Boswellic Acid (AKBBA) inhibits proinflammatory mediators in the body by the primary action of non redox and non competitive inhibition of 5-lipoxygenase. 5- Lipoxygenase catalyses the first two steps in the biosynthesis of leukotrienes and 5-HETE from arachidonic acid, both of which are potent mediators of the inflammatory process (31).

In the Global Evaluation by Physicians (scale of 1 to 10), at the end of 12 weeks, 88.5% of study patients were given an improvement rating of 5 points and over by the Physicians, where 1 indicates bad and 10 indicates good. In the Global Evaluation by Patients' (scale of 1 to 10), at the end of 12 weeks (% improvement), 58.5% of patients mentioned an improvement of over 75% at the end of study.

Consistent reduction of the 'modified' PASI score was witnessed over the course of the study. At baseline, visit 1, the mean 'modified' PASI score was 5.8±0.27. The reduction in the score was significant right from the first visit onwards (P<0.05) according to protocol. It was 4.36±0.22, 3.48±0.17, 2.60±0.14 and 1.78±0.13 at the second, third, fourth and fifth respectively, which was a 24.83%, 40.00%, 55.17% and 69.31% reduction from the baseline percentage.

Several scientific studies have demonstrated without doubt the efficacy of *Boswellia serrata Roxb* in varied chronic inflammatory diseases. It has been put to a novel use in this study; analysis of its efficacy and safety in Psoriasis. Recent studies have also demonstrated its action on platelet type 12-lipoxygenase, and the reversible action of AKBBA on Cox-1 (32).

The present study included 239 patients suffering from psoriasis, of which 39 patients were not included in the final analysis. The resulting 200 patients' average age was 40.74±0.90 with 136 males (68%) and 64 (32%) females completing the study treatment procedures with maximum age being 65 and minimum age being 18. The average weight and height of the study group were 62.49 ± 0.78 kgs and 162.30 ± 0.54 cms respectively, values in mean ± SE. In accordance with our hypothesis we found that *Boswellia serrata* extract standardized for 5% of 95% 3-O-Acetyl-11-Keto Beta Boswellic Acid (AKBBA), showed significant results in the inhibition of inflammatory markers like TNF alpha, VEGF, PGE2 and LTB4, suggesting a molecular role in suppressing chronic inflammatory condition. This positive change confirms the down gradation of the inflammatory pathway of psoriasis. No significant change was seen in the values of MCV, RDW, Monocytes, SGPT and SGOT, their values both at baseline and at the end of the study. The highly significant change in LTB4 values from baseline corroborates with the clinical remis-

sions and photographs suggesting its probable role in the mechanism of action in the alleviation of psoriasis. Global evaluation done by the doctors and the patients illustrates the subjective improvement in symptoms. 84.5% doctors and 58.5% patients gave a rating of over 5 points and 75% improvement respectively. Sixteen patients reported adverse effects out of which 14 patients discontinued the drug. This study was conducted with the approval of Drugs Controller General of India; and many eminent dermatologists from across the country were involved as clinical investigators. Furthermore, the product has been approved for the treatment of mild to moderate psoriasis in 2008 by Central Drugs Standard Control Organization for manufacturing and marketing in India and Sami Labs Limited branded it as Sorosis cream. Limitation of our study includes its open label design and was for duration of 12 weeks. As most of the drugs show their adverse effects over a long period of time, further long term safety studies which are one of the fundamental drug attributes for a chronic disease like psoriasis will therefore be worthwhile exploring.

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CTRI- Clinical Trial Registry (India) Number: CTRI/2013/09/004030

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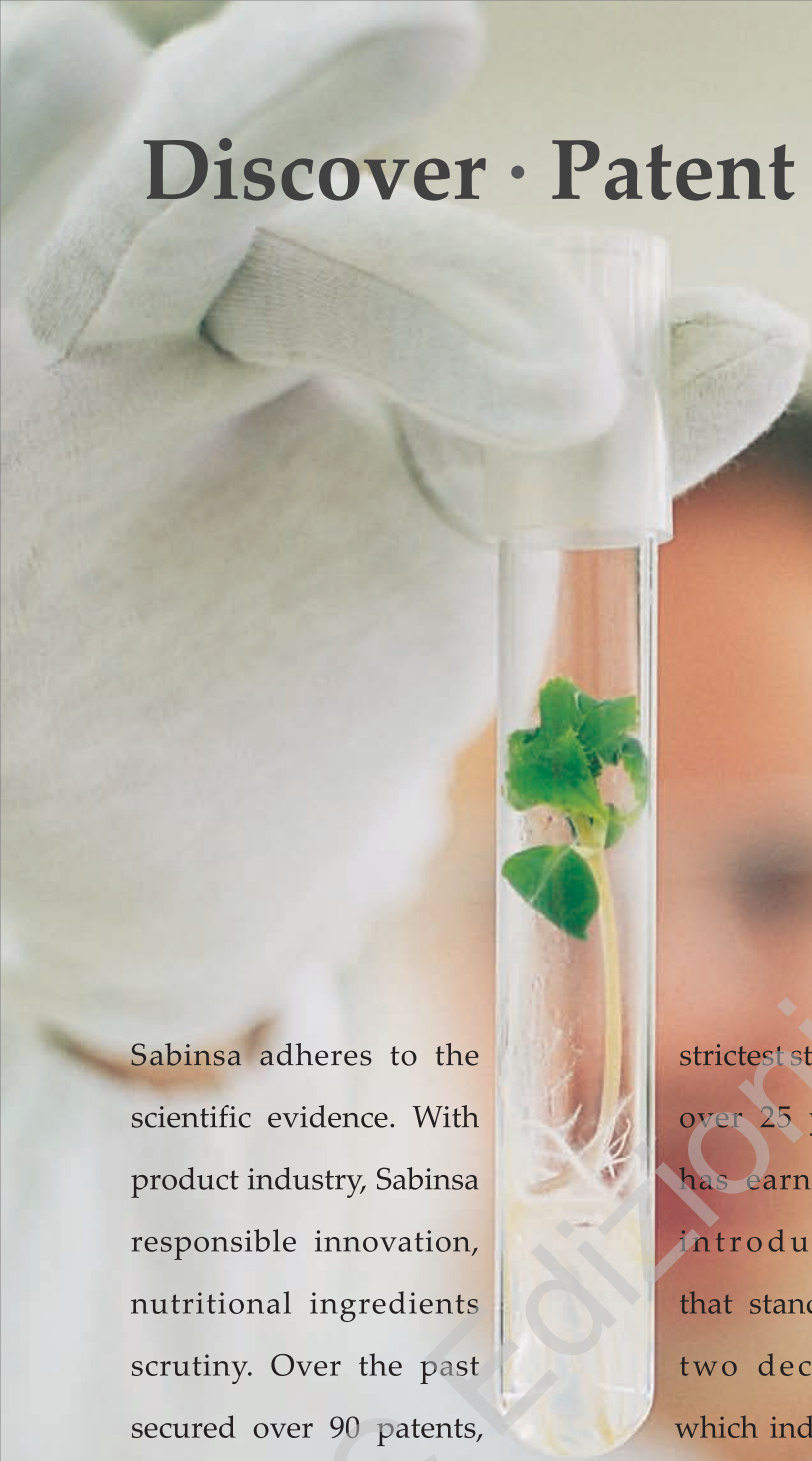

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