Journal of Medical Research and Health Sciences
Received 10 Sept 2022 | Revised 25 Sept 2022 | Accepted 25 Octt 2022 | Published Online 11 Nov 2022

DOI: https://doi.org/10.52845/JMRHS/2022-5-11-1

JMRHS 5 (11), 2324–2328 (2022)

ISSN (O) 2589-9031 | (P) 2589-9023

Research Article **Open Access Journal**

Possible steroidal effect of Boswellia serrata and homeostasis of Histidine – HDC- Histamine in Psoriasis

Aruna V[1], Amruthavalli GV[1], Sumithira Rajakumar[2], Gayathri Rajagopal[1]

Corresponding Author: Aruna V

[1]Dr. JRK's Research and Pharmaceuticals Pvt. Ltd No.18 & 19, Perumal Koil Street, Kunrathur, Chennai- 69

[2]ST.Anne's Arts and Science College Grand Northern Trunk Rd, Kanakan Chatram, Madhavaram, Chennai-110

Abstract

The autoimmune trigger of Psoriasis also takes its share from certain circulating amines released predominantly by mast cell called histamine. The cost of histamine comes certainly with lowered level of the precursor amino acid Histidine which is critical for keeping the skin free of psoriatic expression. The villain who play such ploy of depleting Histidine and the accumulation of Histamine is HDC (Histidine Decarboxylase Enzyme). We have studied HDC inhibition effect of Psorolin B ointment in toto and different herbal ingredients in the formulation. Boswellia serrata exhibited high HDC inhibition effect and the subsequent tests showed that Boswellia serrata does not have any effect of either mast cell degranulation event or in neutralizing Histamine suggesting the enzyme inhibition may be steroidal in nature. The steroid like effect of the above plant has been well established. The details of HDC inhibition assay and the medical and clinical implication of the same in Psoriasis is described in the article.

Keywords: Histamine, Histidine decarboxylase, Boswellia serrata, Psoriasis

Introduction

Psoriasis is indeed a multifactorial disease; has its pathological genesis preserved well in the genetic constitution with transferability, besides the disease that can be poked undeniably by several environmental factors where the susceptible individual lives.[1, 2, 3]

Keratolytic preparations, pro and post inflammatory mediators, mitotic inhibitors, calcitriol and innumerable herbal oils are being used extensively in the treatment of Psoriasis.[4, 5] Keeping the skin in null and void state from clinical expression of Psoriasis is the treatment approach largely followed and practiced by the medical fraternity. The steroidal intervention although may bring some solace to Psoriasis, due to the context of the disease being multifactorial, the cure is always a mirage and often would results in many other unwanted side-effects due to long-term medicament. Long-term medications either with steroid or with other medicaments is needed for Psoriasis.[6, 7]

The exact reason why the disease has gone berserk to dermatology needs courageous debate on the role of an array of several unproven medications which may form an alliance partner to the environmental component of the multifactorial origin of the disease resulting in repeated treatment failure and recurrence. Therefore, the treatment product for the disease like Psoriasis requires greater scientific scrutiny and validation. Otherwise the treatment may gift more harm than the actual disease. We have already established through an elaborate, intense research that most Ayurveda/Siddha oils that are available in the Indian market with *Wrightia tinctoria* for the treatment of Psoriasis have high acid value and such rancid oils bounds to worsen Psoriasis than offer any relief or remission.[8, 9,]

Psorolin B ointment is a Siddha drug formulated with several phyto-pharmaceutical agents from the medicinal plants such as *Wrightia tinctoria, Cynodon dactylon, Boswellia serrata, Hydnocarpus spp.* Further, red ochre is also used in the formulation to support subdermal ferritin requirement as ferritin level in serum is known to decline during active Psoriasis. The clinical evaluation of Psorolin B on plaque psoriasis conducted by us has shown a near complete remission of all signs and symptoms of disease in 12 weeks with no episode of recurrence during our subsequent follow up study for 10 weeks, obviously with continuous usage of Psorolin B ointment.

The resinous constituents of *Boswellia serrata* is proven to have strong steroid like activity by several scientific research work. Further, Boswellia serrata is considered as an apostle by ancient Siddhars and Ayurveda experts for relieving chronic, incurable pain similar to arthritis, inflammation and also various skin diseases.

But the enormous scientific recognition given to the plant Boswellia serrata in the spiritual healing scriptures of Siddha and Ayurveda systems of India clearly show the scientific supremacy and immaculacy of Siddha and Ayurveda systems of medicine.

In the present investigation, we have established HDC (Histidine Decarboxylase) inhibition effect of Boswellia serrata; assumed mostly due to the steroidal nature. Thereby we postulate Psorolin B may make one of the multifactorial origins of Psoriasis mute and thereby may offer the much needed relief to Psoriasis as long as the medication is continued. Details of the findings are presented in the article.

Materials and Methods

HDC assay by sandwich ELISA

We have employed sandwich enzyme immunoassay for the measurement of HDC in cell lysate. Cultured peritoneal mast cells were used for the enzyme source. During growth phase, the mast cells were treated with the test material at different concentrations and then the level of HDC expression in each treatment group was quantified using ELISA technique.

In the present study, the antibody that is specific for HDC was pre-coated onto a microplate. The test samples were pipetted into the wells to allow the HDC present in the test sample to bounds to the immobilized antibody. After subsequent incubation, the unbound sample is removed through a wash step, and then the antibody specific for HDC is added to the wells to bind the HDC in the sample that are already bound to anti-HDC antibody. A coloured product -TMB is formed in proportion to the amount of HDC present in the sample which is measured using microplate reader at 450 nm after doing wavelength correction at either 570 or 630 nm.

Mast cell culture

The peritoneal mast cells were isolated and cultured in DMEM medium with supplements. The extracts of *Wrightia tinctoria, Cynadon dactylon, Hydnocarcpus and Boswellia serrata* were prepared in 1% DMSO in distilled water. The concertation of the test materials used were 10, 20, 30 and 50 µg/ml. After treatment, the mast cells were lysed and then HDC was quantified. The non-treated mast cells were used for HDC comparison to study the role of treatment in HDC production.

By fluorometric method

HDC converts histidine and the resultant product is histamine, is then allowed to react and the resultant product was read for fluorescent signal at

Ex/Em = 535/587 nm. The fluorescent signal is directly proportional to the HDC activity in the samples.

HDC activity assay protocol

The bacterial culture Klebsiella spp., grown overnight at 37 °C was used. Two sets of cultures were maintained viz., one with the test samples in the growth medium and the other set was devoid of the test sample. Then the media broth was centrifuged at 10,000 x *g* for 20 min and then 5 ml ice-cold PBS per 1 gram per cell pellet was added. After which the cells were sonicated for 5 min on ice and again centrifuged at 10,000 x *g* and 4 °C for 20 min. The supernatant (test sample) was transferred in an Eppendorf tube for the assay.

For every test, the following concentrations of the test sample (the supernatant) viz., 10, 20, 30 and 50 µl was added into 96-well plate and then 50 µl per well the HDC assay buffer was also added. HDC assay buffer alone was also maintained as control.

Preparation of histamine standard curve: A standard solution of histamine was prepared and then adjusted accordingly to achieve 0, 50, 100, 150, 200, 250 pmole histamine per well using HDC assay buffer.

Reaction mixture was prepared according the details furnished below

Name of Reaction Mixture	Concentration
HDC Assay Buffer	35 µl
Histidine	10 µl
HDC Enzyme Mix	2 µl
HDC Developer	2 µl
HDC Probe	1 µl

Reading of the fluorescence value of each well taken at Ex/Em= 535/587 nm in kinetic mode at 25 °C for 15-30 min and calculated the result by using the unit definition of 1 unit is 1 µmole of Histamine generated by HDC per min at pH 6.0 and 25 °C.

Results

By Sandwich ELISA, HDC measurement in peritoneal mast cell

The extract of *Boswellia serrata* significantly inhibited the production of HDC in peritoneal macrophage cells and further the activity showed a clear linearity with concentration of the test sample.

None of the other herbal constituents showed any inhibitory effect on HDC production in macrophage cells, Table 1, and so was red ochre.

Table 1 – HDC production versus treatment

Tests	Test sample concentration in µg/ml and HDC in ng/ml			
	10	**20**	**30**	**50**
W.t	50	53	49	54
C.d	55	54	52	55
H.i	54	52	53	51
B.s	38	22	18	11
Red ochre	55	53	53	54
Control	60			

W.t – Wrightia tinctoria, C.d – Cynodon dactylon, H.i – Hydnocarpus idthiyana, B.s – Boswellia serrata

By fluorometric method, HDC measurement in Klebsiella culture broth

The extract of *Boswellia serrata* significantly inhibited HDC production in Klebsella cells whereas other herbal extracts did not exert any such activity, Table 2.

Table 2 – HDC production versus treatment

Tests	Test sample concentration in µg/ml and HDC in ng/ml			
	10	**20**	**30**	**50**
W.t	11	12	11	10
C.d	10	11	11	10
H.i	10	11	11	12
B.s	5	2	1	1
Red ochre	-	-	-	-
Control	15			

Discussion

The positive and negative role of HDC is well known to the medical world. HDC converts the amino acid Histidine to a vasoactive amine, Histamine. The enzyme is largely produced in basophils and macrophage cells. Histamine and its precursor Histidine are extremely essential for human health where the amino acid Histidine regulate metal chelation, achieve redox balance at cellular level, erythropoiesis, glucoregulation, cognition and offer protection to skin from various dermatological problems. The HDC is the only enzyme that could breakdown the amino acid histidine to produce the vasoactive amine Histamine. Under sepsis and other autoimmune and allergic conditions, histamine accumulation takes place and that will result in inflammatory and allergic reaction of the skin. The HDC acts like two headed Janus where it would deplete the amino acid Histidine and simultaneously would also facilitate the over accumulation of histamine.

Psoriasis has multiple etiological triggers where the sedentary, subterranean pathology is elicited to an aggressive proportion by the over expression of HDC and resultant histamine. One of the hypotheses with reference to the origin of Psoriasis is two signal hypothesis where an antigen and secondary stimuli are required for T cell activation. Once T cell is activated, the trigger would in turn elicit the antigen presenting cell in the skin – Langerhans cells to move towards the antigen and then present the same to elicit subsequent immunological action to eliminate the cause. Such subsequent reaction does cause high expression of histamine possibly due to high HDC expression. It is well established that histidine is reversely correlated with pro-inflammatory mediators. The high histamine and high allergic and inflammatory reaction can be linked to low histidine level and possibly high expression of HDC.

HDC suppression is therefore adopted in the treatment of several dermatological conditions. The steroidal preparations, especially betamethasone is known to suppress HDC responsible site. In our present investigation, we found that the resinous constituents of the plant *Boswellia serrata* showed significant effect in suppressing the production of HDC in both peritoneal macrophages as well as HDC producing bacteria Klebsiella spp. The experimental methodology that we adopted clearly suggest the possibility of suppressing the production of HDC enzyme at source than the resinous constituents of *Boswellia serrata* having action of the enzyme activity. The experiment on both peritoneal macrophage and Klebsiella spp., model have provided similar result suggesting the above possibility. In the light of the present findings, we suggest the steroidal action of *Boswellia serrata* resins for the above effect like the steroid Betamethasone. Several earlier studies have clearly shown the steroid like activity of resinous constituents of *Boswellia serrata*.

Considering the histamine accumulation at the cost of histidine depletion where the depletion of histidine is known to negatively impact Psoriasis as well as the accumulation of histamine too is bad for the problem. Histidine depletion and activation of pro-inflammatory mediators are reported and similarly histamine accumulation would increase the inflammatory changes in the system. Therefore, balancing act alone may provide answer to the above biochemical situation and that can be addressed only through either suppressing the production of HDC or reducing the enzyme activity.

None of herbs in Psorolin B had shown any effect on HDC except *Boswellia serrata*. None of the herbs used in the formulation such as *Wrightia tinctoria, Cynodon dactylon or Hydnocarpus spp*., are reported to have any steroid like activity. Therefore, we strongly believe the steroidal activity of *Boswellia serrata* for the above benefit.

In our earlier experiment we have established that Psorolin B had inhibited the release of pro-inflammatory mediators such as INF alpha, IL 8 and IL16 by cultured keratinocytes. The clinical trial findings on small group of Psoriatic patients also showed significant reduction of erythema, inflammatory changes and scaling in 12 week of usage of Psorolin B ointment.

Considering the role of several known and hidden, obvious and inadvertent, direct and convoluted etiological factors of Psoriasis, the treatment approach must be broad and the treatment product must have the pharmacological action towards as many known contributing factor as possible. Only by encompassing the above medical reality and necessity, Psorolin B is formulated. With more and more scientific and therapeutic revelations of Psorolin B for Psoriasis, the day is not far away, Psorolin B will be the first drug of choice of dermatologists across the globe for the treatment Psoriasis.

References

1. Gupta R, Debbaneh MG, Liao W. Genetic Epidemiology of Psoriasis. Curr Dermatol Rep. 2014 Mar;3(1):61-78. doi: 10.1007/s13671-013-0066-6. PMID: 25580373; PMCID: PMC4285384.
2. Capon F. The Genetic Basis of Psoriasis. Int J Mol Sci. 2017 Nov 25;18(12):2526. doi: 10.3390/ijms18122526. PMID: 29186830; PMCID: PMC5751129.
3. Burden A.D., Kirby B. Psoriasis and related disorders. In: Griffiths C.E.M., Barker J.N., Bleiker T., Chalmers R.J., Creamer D., editors. Rook's Textbook of Dermatology. Wiley-Blackwell; Chichester, UK: 2016.
4. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci. 2019 Mar 23;20(6):1475. doi: 10.3390/ijms20061475. PMID: 30909615; PMCID: PMC6471628.
5. Mrowietz U., Kragballe K., Reich K., Spuls P., Griffiths C.E., Nast A., Franke J., Antoniou C., Arenberger P., Balieva F., et al. Definition of treatment goals for moderate to severe psoriasis: A European consensus. Arch. Dermatol. Res. 2011;303:1–10. doi: 10.1007/s00403-010-1080-1.
6. Revicki D., Willian M.K., Saurat J.H., Papp K.A., Ortonne J.P., Sexton C., Camez A. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: Results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br. J. Dermatol. 2008;158:549–557. doi: 10.1111/j.1365-2133.2007.08236.x.
7. Harper R.A. Specificity in the synergism between retinoic acid and EGF on the growth of adult human skin fibroblasts. Exp. Cell Res. 1988;178:254–263.
8. Aruna V, Amruthavalli GV, Soundharya R, Gayathri R, How JRK's 777 oil demolishes the dense, viscous herbal rich oils can be ineffective for psoriasis, Journal of Drug Delivery and Therapeutics. 2020; 10(2-s):105-114 http://dx.doi.org/10.22270/jddt.v10i2-s.3959
9. Aruna V, Gayathri Rajagopal, Rancid Oil: The Hidden Villain of Psoriasis, Research and Reviews: Journal of Unani, Siddha and Homeopathy, STM Journals. 2015; 2(2):22–25
10. Togni S, Maramaldi G, Di Pierro F, Biondi M. A cosmeceutical formulation based on boswellic acids for the treatment of erythematous eczema and psoriasis. Clin Cosmet Investig Dermatol. 2014 Nov 11;7:321-7. doi: 10.2147/CCID.S69240. PMID: 25419153; PMCID: PMC4235203.

How to Cite: V, A. ., Rajakumar, S. ., & Rajagopal, G.. (2022). Possible steroidal effect of Boswellia serrata and homeostasis of Histidine – HDC- Histamine in Psoriasis. Journal of Medical Research and Health Sciences, 5(11), 2324–2328. https://doi.org/10.52845/JMRHS/2022-5-11-1