

Research Article

ENHANCEMENT OF SKIN PERMEABILITY AND ANTI-INFLAMMATORY, ANTIPSORIATIC EFFICACY OF CURCUMIN THROUGH A GEL FORMULATION

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ABSTRACT

Objective: Poor aqueous solubility and permeability of curcumin limits its transdermal absorption. The aim is to increase aqueous solubility and permeability of curcumin by incorporating saponin for better antipsoriatic and anti-inflammatory activity.

Methods: Saponin and Curcumin were procured. Development of formulations of curcumin was done using different concentrations of saponins. Permeation study was conducted by Franz Diffusion cell apparatus. Anti-inflammatory activity on carageenan induced rat paw edema model and antipsoriatic activity on Perry's scientific tail model was conducted. ANOVA applied to analyze data and expressed as Mean \pm SEM ($N = 6$) which was followed by Dunnett's test and differences between means were regarded significant at * ($P < 0.05$), ** ($P < 0.01$) level. Tretinoin 0.025% we found that increase in orthokeratosis.

Results: The Results obtained for Anti-inflammatory activity was found 9.17 % decrease in Cucumin plus saponin gel while only curcumin gel showed 7.74% decrease in paw volume. The results obtained for percentage orthokeratosis found in rat tail skin were 0 %, 4%, 16% , 11 % and 13% for Disease Control, Normal Control, Standard Drug (Tretinoin sulphate), Curcumin and Curcumin plus Saponin gel formulation respectively. Curcumin and Saponin gel formulation might play crucial role in anti-inflammatory and antipsoriatic activity.

Conclusion: It has been concluded that the novel formulated gel containing curcumin and saponin shows good anti-inflammatory and antipsoriatic activity in rat models.

Keywords: Curcumin , saponin , herbal gel, anti-inflammatory, antipsoriatic

INTRODUCTION

Psoriasis is an autoimmune illness exemplified by elevated red, white, or silvery skin patches (Fig 1)^[1]. Psoriasis is a widespread skin disease, chronic inflammatory that affects roughly 0.5%–1% of kids and 2%–3% of the global population ^[2, 3]. Hereditary and environmental factors play a major part in the pathogenesis of this non-contagious skin ailment. It influences about 1.5% of the globally^[4]. Although seldom serious, psoriasis is related with considerable morbidity and is believed by to be an sensitively crippling disease ^[2, 5].



Figure 1: Psoriasis of knee joint as point out by red, silvery lesions, a hallmark of this disease.

The activated T-cells release cytokines, that speed up epidermal cell turnover and alters in the keratinocytes and skin vasculature. These modifications eventually

develop to the characteristic psoriatic lesions [6]. Existing management of Psoriasis and disadvantages in transdermal delivery of Curcumin: Mild psoriasis is usually managed with topical therapy (Tretinoin) [7]. Although, a systemic treatment such as methotrexate, cyclosporine, retinoids, or phototherapy (ultraviolet B, psoralen plus ultraviolet A) has been given for moderate to severe psoriasis [1]. We suppose that, curcumin a renowned anti-inflammatory agent derived from *Curcuma longa* holds promise in management of psoriasis. *Curcuma longa* (turmeric) is a spice and a medicinal herb with an extensive account of use as a management for inflammatory conditions in Asia [8, 9]. Turmeric phytoconstituents contains three curcuminoids (demethoxycurcumin, curcumin, and bisdemethoxycurcumin), volatile oils (tumerone, natlantone and zingiberone), proteins, sugars and resins. It controls swelling, cell growth and apoptosis, due to its anti-oxidant property most of which are attributed to the presence of curcumin. Curcumin has been shown to be a highly pleiotropic molecule related to many inflammatory molecular targets [10]. Due to its important properties, approximately many companies are at present offering different curcumin products in the form of various formulations for both edible and medical needs [11]. For the efficient topical treatment of psoriasis, the anti-inflammatory agents have to be delivered to the activated immune cells present in the skin. Conversely, skin presents an alarming hurdle to the penetration of many drugs [12] and the granular layer of the epidermis is decreased. Although normal skin has notable numbers of resident and trafficking immune cells (and is an immune-competent organ), in psoriatic lesions the leukocyte number is significantly increased and many immune-related pathways are activated [13].

However, skin presents a formidable barrier to the permeation of many drugs, such as curcumin. The skin consists of main layers (Fig. 2). First is the epidermis, that mainly consists of keratinocytes [14].

In psoriasis, cells of the stratum corneum (the outermost layer of the epidermis) produce unusually, leading to the formation of scales. Through gel formation we have prepared five different formulations containing varying concentrations of carbopol 934 found that optimal concentration was 0.45% carbopol 934 produced homogeneous gel formulation. P^H was adjusted up to 6 by using triethanolamine. Curcumin hydrogel shows good anti-inflammatory activity in rats [22]. Garlic and turmeric dried crude extract shown synergistic antifungal activity [23]. Curcumin gel produced from curcumin solid lipid nanoparticles used to treat collagen induced rheumatoid arthritis in rats [24].

Saponins having immunomodulatory activity. Saponins are derived from natural sources having amphiphilic nature owing to presence of hydrophilic sugars conjugated to hydrophobic triterpenes or steroids. Sapogenin present in saponin responsible for surfactant activity [20].

The saponin molecules consist of a hydrophobic region, called aglycone, which is associated to one or several oligosaccharide (sugar) chains that make the hydrophilic part of the molecule [21].

Poor aqueous solubility and permeability of curcumin limits its transdermal absorption. The aim of the current research work is to increase aqueous solubility and permeability of curcumin by incorporating saponin for better antipsoriatic and anti-inflammatory activity.

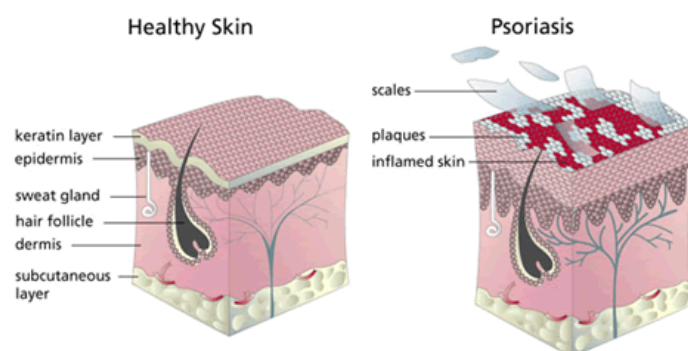


Fig. 2 Differences in the histology of normal and psoriatic skin.

MATERIAL AND METHODS

2.1 Procurement of plant materials: Saponin and Curcumin was procured from the supplier.

2.2 Formulations of curcumin:

- Curcumin (2 % w/w gel) and olive oil (2 % w/w) formulation shows good permeation through artificial and rabbit skin [22].
- Through gel formation we have prepared five different formulations containing varying concentrations of carbopol 934 found that optimal concentration was 0.45% carbopol 934 produced homogeneous gel formulation. P^H was adjusted up to 6 by using triethanolamine.
- Curcumin hydrogel shows good anti-inflammatory activity in rats [22].
- Garlic and turmeric dried crude extract shown synergistic antifungal activity [23].
- Curcumin gel produced from curcumin solid lipid nanoparticles used to treat collagen induced rheumatoid arthritis in rats [24].

- f. Curcumin and nyctanthes abortris leaves extract found antimicrobial activity^[25].
- g. Herbal ointment containing Neem and Turmeric extract ^[26].

2.3 Biphasic formulation of curcumin using saponins:

Various formulations of curcumin were prepared using varying concentrations of saponins.

After finalizing the concentration of carbopol 934 (0.45 %) made two formulations containing 0.1 % and 0.2 % saponin. Propylene glycol (2ml), Distilled Water q.s. to make 100ml and Triethanolamine was added till it forms gel. Evaluation was done by using franz diffusion cell apparatus.

pH- Direct measurements were made using a digital pH meter .

Spreadability test- Gel should spread easily without too much drag and should not produce greater friction in the rubbing process. Spreadability was calculated using the spreadability apparatus made of wooden board with scale and two glass slides having two pans on both sides mounted on a pulley.

Appearance and homogeneity - All developed gels were tested for physical appearance and homogeneity by visual observation.

Stability- Stability of curcumin and curcumin- Saponin gel were compared with standard curcumin by using Chloroform : Ethanol : Glacial A. A. (95:5:1), vanillin, sulphuric acid reagent system.

2.4 In vitro Evaluation of transdermal permeation enhancement

Franz diffusion Permeation study by using rat abdominal skin as in vitro model-

Skin permeation was assayed by Franz cell apparatus. Throughout experiment 1.5 mL aliquots of receptor solution were collected at 30 min, 1hour, 2hour, 3 hour, 4 hour, 5 hour, 6 hour, 7 hour, and 8 hour for spectrophotometric analysis at 425 nm.

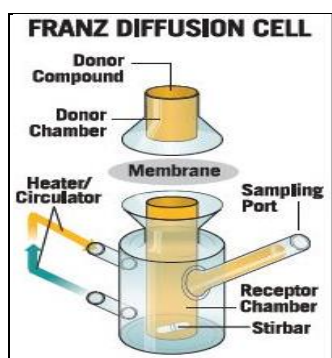


Fig. No.3 : Franz diffusion cell apparatus;

2.5 Anti-inflammatory activity (Carrageenan rat model) .

Animal preparation (Protocol was approved by IAEC of SMBT College of Pharmacy, Dhamangaon) 6

animals per cage (Wist. Alb. Rat 180-200g) provided facilities as per CPCSEA guidelines.

Carrageenan induced rat paw edema

For Carrageenan induced rat paw edema, Pedal inflammation was induced in rats as explained by Winter *et al.* (1962). A suspension of 0.05 ml of 1% Carrageenan was injected into the sub plantar tissue of right hind paw of each rat. The paw volume was measured at 0, 1, 2, 3 and 4 h using Plethysmometer (UGO Basile, Italy) (Vogel and Vogel, 2002). Difference in paw volume was calculated. Marketed (Dicofenac 1% w/w gel) Omnigel, Nise gel and test formulations applied topically (surface of the hind paw by gently rubbing 50 times with the index finger) as reference drug. Anti-inflammation effect was calculated as percentage of edema volume inhibition. The percentage of edema inhibition calculated as:

$$\text{Inhibition of edema volume (\%)} = \frac{\text{VNC} - \text{VT}}{\text{VNC}} \times 100\%$$

Note:

VNC=mean increase in paw volume in negative control groups

VT=mean increase in paw volume in treated groups ^[27].

2.6 Antipsoriatic activity by Perry scientific tail model

This is conventional as screening method for determining antipsoriatic activity of drugs. This model depends on topical treatment of tail with antipsoriatic agents which enhances orthokeratotic cell separation in the epidermal scales ^[7].

Tretinoin 0.025% cream U.S.P (Cadila Pharmaceuticals Ltd.) was used as a standard.

Procedure

Male Wistar rats 250-300 g weight were used in experiment. End of tail, an area on one side of the edge is exposed for 20 min (1.5 J/cm²) at a vertical distance of 20 cm with UV lamps. A biphasic erythema is detected. Instantly post irradiation, early faint erythema looks, fading within 30 min. The second phase of erythema starts 6 h after the irradiation and gradually increases, peaking between 24 and 48h. The color is brownish-red, and the reaction is confined to the exposed area with a sharp boundary. By 48-72 h after irradiation, dark brown scale is formed on the erythematous lesion. Pieces of the scale are comparatively thick.

Method of screening

Standard and test gels were useful locally, one time in a day, five times a week, for 2weeks. Animals were sacrificed after treatment in 2 h, longitudinal sections of the tail skin were made and set for histological examination (hematoxylin- eosin staining) as an indicator of orthokeratosis the number of scale regions with a continuous granular layer is counted and

expressed as a percentage of the total number of scale area per section. Drug activity is defined by the increase in percentage of orthokeratotic regions.

Statistical data analysis.

Statistical analysis was carried out by one way ANOVA test [27].

3.1 Curcumin gel formulation with varying concentrations of carbopol evaluated for Physical appearance, PH, Homogeneity and Spreading Diameter (cm)

Percentage decrease in Curcumin plus saponin gel shown 9.17 % decrease in paw volume while only curcumin gel shown 7.74% decrease in paw volume.

RESULTS

Table No. 1: Curcumin gel formulation with varying concentrations of carbopol 934
Curcumin 2% in each formulation from F1 to F5

Formulation/ Batch	Concentrations of carbopol 934 (%)	Physical appearance	PH	Homogeneity	Spreading Diameter (cm)
F1	0.25%	opaque	5.99	Viscous solution	7.0 ± 0.2
F2	0.35%	opaque	6.02	Viscous solution	7.2± 0.3
F3	0.45%	opaque	5.95	Homogeneous gel	7.5± 0.1
F4	0.55%	opaque	5.94	Homogeneous gel	7.5± 0.3
F5	0.65%	opaque	5.96	Homogeneous gel	7.5± 0.2

3.2 Absorption found by using U.V. spectroscopic analysis at 425nm.

Table No.2: Absorbance of formulations

Time in Min.	F1	F2	F3	F6(Saponin 0.1%)	F7(Saponin 0.2%)
30	0.98	1.02	1.36	2.65	2.78
60	5.56	6.22	7.41	9.12	9.5
120	10.12	10.98	13.69	18.09	18.6
180	15.69	16.66	20.37	28.77	28.66
240	28.49	29.3	28.86	44.03	45.1
300	30.5	31.66	36.91	55.40	56.21
360	40.22	40.01	45.05	66.55	66
420	52.3	51.95	54.21	77.00	77.8
480	60.28	60.07	64.35	78.00	79.01

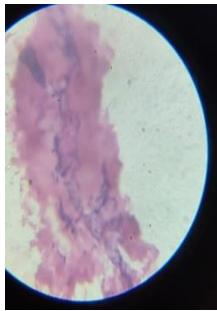
We found that no significant difference in 0.1 and 0.2% of Saponin containing formulation.

3.3 Anti-inflammatory activity

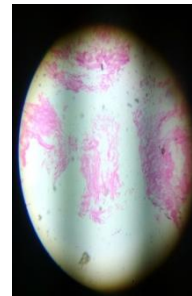
Table 3: Paw edema volume after treatment

Groups/ Time	0Hr	1Hr	2Hr	3Hr	4Hr	% Decrease in paw volume
Normal	1.274± 0.025*	1.28±0.015*	1.286±0.013*	1.29±0.014*	1.216±0.018*	13.09%
Disease Control	1.592±0.009*	1.608±0.02*	1.53±0.01*	1.588±0.028**	1.58±0.03*	0.99%
Nise Gel	1.028±0.038**	1.21±0.028*	1.306±0.032**	1.438± 0.017**	1.390.017**	18.06%
Omnigel	1.246± 0.017*	1.334±0.029*	1.394±0.042**	1.382±0.029*	1.2740±.017*	14.83%
Curcumin	1.342± 0.029**	1.36± 0.038**	1.48± 0.030**	1.594± 0.016*	1.4120.024*	7.74%
Curcumin+ Saponin	1.038±0.038**	1.31±0.028*	1.356±0.032**	1.238± 0.017**	1.190.017***	9.17%

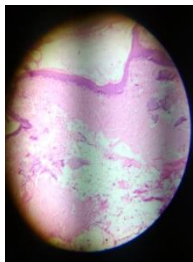
ANOVA applied to analyze data and expressed as Mean ± SEM (N =6) which was followed by Dunnett’s test and differences between means were regarded significant at * (P< 0.05), ** (P< 0.01) level.



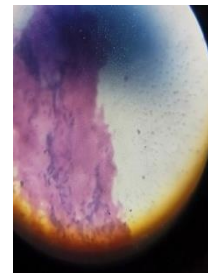
A. Normal Control 4% orthokeratosis found in normal rat tail skin.



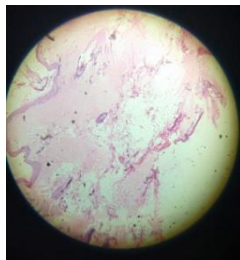
B. Disease Control- No orthokeratosis found in disease control rat tail.



C. Standard Drug (Tretinoin sulphate) 1 6% orthokeratosis



D. Curcumin treated shows 11% orthokeratosis



E. Curcumin + Saponin 13% orthokeratosis

Fig. 2 % orthokeratosis rat tail skin after antipsoriatic treatment

3.4 Histopathology of rat tail skin after antipsoriatic treatment

After induction of psoriasis rat tail was treated with curcumin gel, curcumin and saponin gel, Tretinoin 0.025% we found that increase in orthokeratosis with reference and test formulations.

4. DISCUSSION:

Curcumin is that the key solely active polyphenolic constituent in turmeric. Curcumin exercises a large range of beneficial physiological and pharmacological actions. Though, its poor solubility and deprived absorption within the morpheme within the channel and its quick metabolism to inactive metabolites intensely limit its usefulness as a health-promoting agent and dietary supplement [28]. The novel idea of adding chemotherapy or treating ordinary medical

conditions with a conventional spice could be a stimulating to this point challenging pace in medicine. Curcumin could be an intense yellow matter isolated from turmeric L. (turmeric) plants (Zingiberaceae). Numerous pharmacological properties, of curcumin were evaluated. [29]. Saponin could be a natural detergent for laundry the body, hair, and garments, and it's used as a usual surfactant [30]. Saponins include an outsized a steroid or triterpenoid aglycone (sapogenin) associated to a minimum of one or more oligosaccharide moieties [31]. Although it's going to represent by dissimilar clinical variants, the foremost commonly described is that the "vulgaris" one, which is characterized by erythematous round or oval abrasions, enclosed by white-silvery scales. Cutaneous abrasions are usually limited to atiny low area on the knees, elbows, and scalp lumbosacral region, also they will affect different body parts [32]. In spite of the accessibility of unlike topical and systemic therapeutic choice for the treatment of psoriasis, none of them

offers outstanding clinical results with no the danger of side effects [33]. Recently, Kang D. *et al.* have confirmed, on mice models, one more significant effect of curcumin, consisting within the inhibition of the potassium channels (subtypes Kv1.3) articulated on T cells, which seem to be involved within the onset of psoriasis. The anti-inflammatory activity of curcumin, is confirmed by the finding that mice, showed in their serum a decrease of quite 50% level of inflammatory factors, including TNF - α , IFN - γ , IL - 2, IL - 12, IL - 22 and IL - 23[34]. Isolated skin from inbred animals like rodents (guinea pig, rat, and mouse); rabbit; and shed snake skin are routinely considered as option to human skin, as they'll be got easily, will be removed fresh before skin permeation studies with viability and enzymatic activity, and exhibit less variability [35]. Carrageenan-induced edema is sometimes used experimental model for evaluation of acute inflammation in animals. Carrageenan, when injected into the sub-plantar region of rat's paw, produces inflammatory reaction (edema) that's visible within 30 min. The presumptive mechanism of action of carrageenan induced edema has been found to be biphasic. The first phase (1-2 h) is because of the liberation of 5-hydroxy tryptamine, histamine and bradykinin, while the second phase is attributed to the discharge of prostaglandins. Carrageenan-induced paw edema and cotton pellet granuloma formation in rats reflect the edematous stages during acute and chronic inflammation [36]. Studies including clinical trials have demonstrated the effectiveness of natural products on decreasing proinflammatory responses in many diseases [37].

In our study Anti-inflammatory activity of prepared gel was found to be more significant as compared to plain curcumin gel. The Results obtained for Anti-inflammatory activity was found 9.17 % decrease in Cucumin plus saponin gel while only curcumin gel showed 7.74% decrease in paw volume. The results obtained for percentage orthokeratosis found in rat tail skin were

0 %, 4%, 16%, 11 % and 13% for Disease Control, Normal Control, Standard Drug (Tretinoin sulphate), Curcumin plain and Curcumin + Saponin gel formulation respectively. It has been concluded that the novel formulated gel containing curcumin and saponin shows good anti-inflammatory and antipsoriatic activity in rat models. Our work has revealed the scope and potential of curcumin and saponin gel formulation. We can also explore this work by using *in vitro* models.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Authors' contributions

PGM and MRK initiated the idea, contributed in the experimental work and wrote down the manuscript. SJS and CMD conducted the experimental work, read and accepted the final manuscript. PGM and MRK prepared the gel formulations and tested, read and approved the

final manuscript. PGM, MRK and CMD participated in the experimental work, PGM and MRK revised and edited the manuscript.

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