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A Curcumin-Nanosized Invasome Topical Formulation Evaluated Against Anti-inflammatory activity in Wistar rat

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Abstract

The current pharmacological research was to explore the anti-inflammatory activity of a curcumin-nanosized invasome topical formulation in Wistar albino rodents. In this research, two methods were used: the carrageenan-induced paw edema method and the cotton pellet-induced granuloma test. Results of the carrageenan-induced paw edema test showed that invasomal gel at doses of 720 g/100 g (25 mg of gel) reduced the paw volume significantly (p 0.01) as compared to the control at 3 hr. volume. A reduction in paw edema was found in 15.09% of treated animals. Diclofenac sodium reduced maximum paw edema by 41.5%, and a cotton pellet-induced granuloma test showed a marked protection in granuloma by invasomal gel, which markedly reduced the dry weight and the wet weight of the cotton pellet at a dose of 720 g/100 when compared to the control. The standard diclofenac gel produces maximum activity by inhibiting the wet weight and dry weight of the cotton pellet, respectively, by 27.41% and 40.93%. The dose of invasomal gel showed a significant reduction in the wet weight and dry weight of cotton pellets at 9.07% for 720 g/100 g. It was observed that the invasomal gel at a dose of 720 g/100 produced significant anti-inflammatory activity.

Keywords- Invasomal gel, Anti-inflammatory activity, Granuloma, Carrageenan-induced paw edema.

INTRODUCTION-

Invasomes are novel vesicular systems that exhibit improved transdermal penetration compared to conventional liposomes. These vesicles contain phospholipids, ethanol, and terpene in their structures; these components confer suitable transdermal penetration properties to the soft vesicles. The main advantages of these nanovesicles lie in their ability to increase the permeability of the drug into the skin and decrease absorption into the systemic circulation, thus, limiting the activity of various drugs within the skin layer [1,2].

Turmeric is a spice that has received much interest from both the medical/scientific worlds as well as from the culinary world. Turmeric is a rhizomatous herbaceous perennial plant (Curcuma longa) of the ginger family. The medicinal properties of turmeric, the source of curcumin, have been known for thousands of years; however, the ability to determine the exact mechanism(s) of action and to determine the bioactive components have only recently been investigated. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane, is the main natural polyphenol found in the rhizome of Curcuma longa (turmeric) and in others Curcuma spp. Curcuma longa has been

traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer properties[3,4].

Inflammation is the body's protective mechanism elicited in response to mechanical injuries, microbial infections, burns, and other deleterious stimuli that may threaten the host health [5]. It can be classified as either acute or chronic inflammation. Acute inflammation occurs as an immediate response to trauma, usually between two hours while chronic inflammation occurs as an ongoing response to a longer-term medical condition [6,7]. Chronic inflammation has been claimed to cause the most significant death in the World [8]. Clinically, inflammation is defined as a pathophysiological process characterized by pain, redness, edema, heat, and loss of tissue function [9]. This process involves changes in blood flow, increased permeability of vascular tissues, and tissue destruction via the activation and migration of leucocytes with the synthesis of reactive oxygen species (ROS), and local inflammatory mediators, including prostaglandins, leukotrienes, and platelet-activating factors induced by phospholipase A2, cyclooxygenases, and lipoxygenases [10,11].
Conventional steroidal anti-inflammatory drugs and non-steroidal anti-inflammatory drugs (NSAID) used in the treatment of acute inflammatory disorders have been unsuccessful in the treatment of chronic inflammatory disorders including rheumatoid arthritis. These conventional anti-inflammatory drugs have also been associated with unwanted side effects [12,13]. This has led to the search for an alternative remedy, especially from medicinal plants to treat these inflammatory disorders. Therefore, the aim of this study was to evaluate the anti-inflammatory effects of MEJSL, using in vitro and in vivo inflammation models with the rationale to provide an insight into the potential anti-inflammatory mechanisms of action.

MATERIALS AND METHODS

1) Experimental Rodents

The experiment was carried out on Wistar albino rats of 4 months, of both sexes, weighing between 100 to 150gm. They were provided from College of Pharmaceutical sciences, Barpali, Odisha. The animals were acclimatized to the standard laboratory conditions in cross ventilated animal house at temperature 25±2°C relative humidity 44 –56% and light and dark cycles of 12:12 hours, fed with standard pallet diet and water *ad libitum* during experiment. The experiment was approved by the institutional ethics committee and as per CPCSEA guidelines (approval no. IAEC/2019-20/RP-06).

2) Drugs and Chemicals

Diclofenac sodium was obtained from Micro Labs Limited and Carrageenan from Sigma Aldrich.

3) Study Protocol

Carrageenan-induced rat paw edema

Acute inflammation was caused by injecting 0.1 ml carrageenan (1 % w/v in saline) into the sub-plantar region of the left hind paw of each rat. The paw volume was measured plethysmometrically at 0 h, 1 h, 2 h, 3h, and 4h after the carrageenan injection. Edema was expressed as mean increase in paw volume relative to control animals. The percentage inhibition of edema was calculated by the following equation:

% Inhibition of edema= 100 (1-Vt/Vc),

where Vc is the edema volume in the control group and Vt is the edema volume in tested groups. [14].

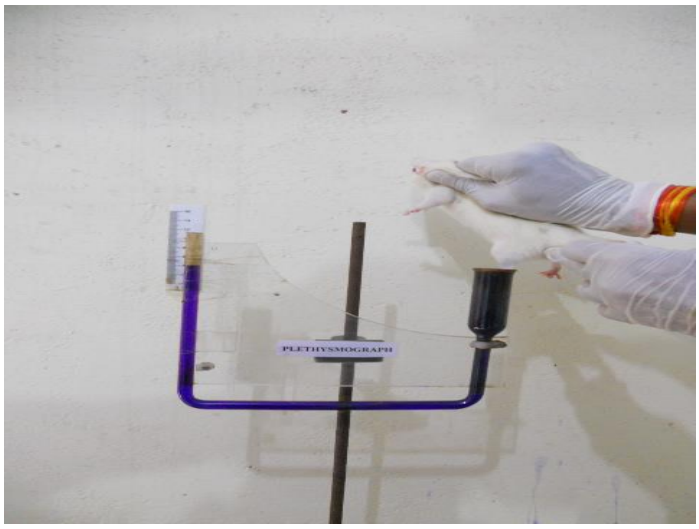

Fig 1.Measurement of paw volume by Plethysmograph

Grouping and dosing:

In the experiment, a total of 18 rats were used. The rats were divided into 3 groups comprising of 6 animals in each group as follows:

Group **I:** control rats received Gel base before 1hr of carrageenan injection.

Group **II:** Rats treated with Diclofenac sod. gel720 µg/100 g (25 mg of gel).

Group **III:** Rats treated with invasomes gel (25 mg/kg p.o.) before 1hr of carrageenan injection.

Cotton pellet-induced granuloma in rats

Cotton pellets were prepared of 10±0.5 gm weight by weighing the raw cotton on weighing balance and rolling then in a pellet shape. The pellets were kept in an oven for 30 min for sterilization. Hairs of back of animals were removed using hair removal cream. Animals were anaesthetised. With the help of surgical blade, an incision was given in the scapular region. By using artery forceps, subcutaneous tunnels were formed to place sterilised cotton pellets on both sides of scapular region. Incisions were sealed with the help of tissue adhesive. Animals were treated for 7 days. On 7th day, animals were sacrificed by cervical dislocation and removed the pellets. Pellets were weighed separately. Weight of these pellets refers to the wet weight of granuloma plus weight of the cotton implanted. For dry weight, pellets were placed in oven for 18 hrs at 60 ^{0}C. Pellets were removed from oven and dry weight was measured. The percentage inhibition of the wet weight and dry weight of the granuloma were calculated and compared[15].

The percent inhibition in the weight of the cotton pellets was calculated by:

% Inhibition = [Wc–Wt/Wc] × 100

Where,

*W*t is granulation weight in treated groups

*W*c is granulation weight in control group

Grouping and dosing:

In the experiment, a total of 18 rats were used. The rats were divided into 3 groups comprising of 6 animals in each group as follows:

Group **I:** control rats received Gel base720 µg/100 g (25 mg of gel) for 7 days.

Group **II:** Rats treated with Diclofenac sod. 720 µg/100 g (25 mg of gel)for 7 days.

Group **III:** Rats treated with invasomal gel720 µg/100 g (25 mg of gel) for 7 days.

Statistical Analysis

The statistical analysis was completed utilizing Graphpad 5.0 software. Data were noted as mean ± S.E.M. The statistical consequence of variation between groups was concluded by analysis of different two way (ANOVA) followed via Bonferroni posttests. Differences of P<0.001 were examining statically indicative

RESULTS AND DISCUSSION

Anti-inflammatory study

Effect of Invasomal gel on carrageenan induced paw edema in Albino Wistar rats

Inflammatory reaction is readily produced in rats in the form of paw edema with help of irritants like carrageenan, formalin, bradykinin histamine, etc. when injected in dorsum of foot, they produce acute paw edema. Carrageenan-induced paw edema is the standard experimental model for acute inflammation in experimental animals.

Anti-inflammatory evaluation study conducted on 3 different group of male wistar rat by carrageenan induced paw edema method. Reduction in the edema was evaluated by calculating the mean paw volume after induction of solution to different group for 0 min, 1hr, 2hr, 3hr and 4hr. Results of Carrageenan-induced paw edema test showed that invasomal gel at doses 720 µg/100 g (25 mg of gel)reduced the paw volume significantly (p<0.01) as compared to control at 3 hr. volume. Reduction in paw edema was found 15.09% in treated animals. Diclofenac sodium reduced maximum paw edema by 41.5% (table 1).

Table 1 - Effect of invasomal gel on carrageenan induced paw edema in rats.

Groups	Paw volume (mm) (Mean±SEM)					% Inhibition
	0hr	1 hr	2 hr	3hr	4hr	
I	0.26±0.04	0.4±0.041	0.43±0.04	0.51±0.048	0.53±0.057	-
II	0.28±0.04 20	0.33±0.04	0.31±0.041	0.33±0.047[a**]	0.31±0.051 [a**]	41.5
III	0.28±0.04 2	0.28±0.042	0.35±0.044	0.4±0.042	0.45±0.054	15.09

All values are mean ± SEM, n = 6. $^{*}p<0.05$, $^{**}p<0.01$,

a- Significance difference as compared to control

b- Significance difference as compared to standard

Effect of Invasomal gel on Cotton pellet-induced granuloma in rats

The results of cotton pellet-induced granuloma test showed a marked protection in granuloma by invasomal gel, which markedly reduced the dry weight and the wet weight of the cotton pellet at dose of 720 µg/100 when compared to control. The standard diclofenac gel produces maximum activity by inhibiting the wet weight and dry weight of the cotton pellet, 27.41% and 40.93 % respectively. The dose of invasomal gel showed significant reduction of wet weight and dry weight of cotton pellet at 9.07% for 720 µg/100 g. It was observed that the invasomal gel at dose of 720 µg/100 produced a significant anti-inflammatory activity by reducing the dry weight and wet weight granuloma but lower than the standard drug diclofenac (Table 2)

Table 2: Effect of Invasomal gel on wet weight and dry weight of cotton pellet in Cotton pellet-induced granuloma rats.

Group No.	Treatment	Wet weight of cotton pellet (mg) (Mean±SEM)	% Inhibition in wet weight	Dry weight of cotton pellet (mg) (Mean±SEM)	% Inhibition in dry weight
I	Control	90±2.65	-	32.17±1.73	-
II	Standard	65.33±2.75[a***]	27.41	19.0±1.75 [a***]	40.93
III	Invasomal gel	81.83±2.88 [a*, b***]	9.07	30.67±1.7[b***]	4.66

All values are mean ± SEM, n = 6. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

a- Significance difference as compared to control

b- Significant difference as compared to standard

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Declarations

Conflict of Interest -The authors declare no potential conflicts of interest.

Ethical Approval - The experiment was approved by the institutional ethics committee and as per CPCSEA guidelines (approval no. IAEC/2019-20/RP-06).

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