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DESIGN, DEVELOPMENT AND EVALUATION OF TOPICAL ANTIINFLAMATORY HERBAL GEL

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ABSTRACT: The objective of the present investigation was to develop topical curcuminoids containing gel as an anti-inflammatory. The first gel base was prepared by using various different concentrations of Carbopol 934, Propylene glycol 400, Methylparaben, Propylparaben, and required amount of distilled water. The optimized base was selected for the incorporation of different concentrations of curcuminoids (CM) and fixed concentration of tulsi oil (TO) and eucalyptus oil (EO). Then skin pH (6.8-7) was maintained by the dropwise addition of tri-ethanolamine. Prepared formulations were evaluated for physical appearance, pH, spreadability, viscosity, and homogeneity. Prepared formulations have proceeded for skin irritation on an animal model (rabbit). All gels were evaluated for anti-inflammatory activity by using carrageenan-induced rat paw edema model on Albino Wistar rats of either sex (150-200 gm). Change in edema volume of the rat hind paw was measured, and percent inhibition was calculated. Stability studies have carried out as per ICH guidelines for 3 months at different temperatures and humidity. Results reveal that all formulations have shown good appearance, homogeneity, and spreadability. The viscosity of all formulations is ranging between 4000-4500 centipoises. All formulations have shown no skin irritation, *i.e.*, erythema and edema to animals. Formulations F3 and F4 significantly inhibited the inflammation to the extent of 26.83%, 43.90% at 3 h, and 37.78%, 57.77% 4 h, respectively, while the reference drug; diclofenac sodium reduced the inflammation by 60.97% at 3 h and 73.33% at 4 h. The anti-inflammatory effect of F4 formulation was comparable to that of diclofenac sodium at the respective time point.

INTRODUCTION: Inflammation is a complex process, which is frequently associated with pain and involves occurrences such as the increase of vascular permeability, increase of protein denaturation, and membrane alteration.

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When cells in the body are damaged by microbes, physical agents or chemical agents, the injury is in the form of stress. The inflammation of tissue is due to the response to stress. It is a defensive response that is characterized by redness, pain, heat, and swelling and loss of function in the injured area.

Inflammation is one of the body's nonspecific internal systems of defense, the response of a tissue to an accidental cut is similar to the response that results from other types of tissue damage caused by burns due to heat, radiation, bacterial or viral

invasion. Inflammation dilutes, destroys, or walls off harmful agents that have entered the body. It activates a sequence of biological events to heal the damage. The most common causes of inflammation are infections, burns and trauma, and many types of immune reactions [1, 2].

Curcuminoid is linear, diarylheptanoid molecules that include curcumin and related compounds. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione), also called diferuloyl-methane, is the main natural polyphenol found in the rhizome of *Curcuma longa* (turmeric) and in others Curcuma spp. The turmeric plant *C. longa* naturally possesses two major congeners of curcumin namely demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC). Curcumin is a yellow-orange hydrophobic compound insoluble in water and ether but soluble in dimethylsulfoxide, acetone, ethanol, and oils.

It generically consists of two ferulic acid residues joined by a methylene bridge. A less common analog of curcumin, cyclocurcumin, is also naturally found in *C. longa* although in low proportions. Curcumin is widely documented as an anti-inflammatory with relevance for chemoprevention and has been suggested to modulate eicosanoid biosynthesis and to inhibit COX-1, COX-2, and LOX. Curcuminoid is reported in a reduction of blood cholesterol level, prevention of low-density lipoprotein (LDL) oxidation, inhibition of platelet aggregation, suppression of thrombosis and myocardial infarction.

It is also used in the suppression of symptoms associated with type II diabetes, rheumatoid arthritis, multiple sclerosis and Alzheimer's disease, inhibition of human immunodeficiency virus (HIV) replication. Curcuminoid used in the enhancement of wound healing, an increase of bile secretion, protection from liver injury, cataract formation and pulmonary toxicity and fibrosis, an exhibition of anti-leishmaniasis and anti-atherosclerotic properties, as well as prevention and treatment of cancer. Curcumin inhibits the metabolism of arachidonic acid, activities of cyclooxygenase, lipoxygenase, cytokines (interleukins and tumor necrosis factor), nuclear factor-κB (NF-κB) and release of steroids [3-10].

Eucalyptus (*Eucapyptus* spp.), is a large genus of the Myrtaceae family, which includes 900 species and subspecies. *E. globulus* is a rich source of phytochemical compounds like flavonoids, alkaloids, tannins, and propanoids, extracted in the leaf, stem, and root of the plant. Several volatile constituents as 1, 8-cineole (eucalyptol) aromadendrene, αgurjunene, globulol, ß-pinene, pipertone, α-, β-and γ-terpinen-4-ol, and allo-aromadendrene were found both in leaves and in shoots. Borneol, caproic acid, citral, eudesmol, fenchone, p-menthane, myrecene, myrtenol, α-terpineol, verbinone, asparagine, cysteine, glycine, glutamic acid, ornithine, and threonine were extracted from fruits. The oil is extracted from leaves, fruits, buds and bark showing antibacterial, antiseptic, antioxidant, anticancer activities and for this reason used in the treatment of respiratory diseases, common cold, influenza, and sinus congestion.

The aromatic constituents of EO are used as an analgesic, anti-inflammatory, and antipyretic remedies. The role of eucalyptol as inhibitor of the production and synthesis of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), leukotriene B4, and thromboxane B2 in human blood monocytes, suggesting that eucalyptol is a strong inhibitor of cytokines that might be suitable for long term treatment of airway inflammation in bronchial asthma and other steroid-sensitive disorders. These results should help to clarify functional applications for the future of eucalyptus plant and its EO in anti-inflammatory treatments [11-18].

Ocimum sanctum L., known as ‘Tulsi’ in Hindi and ‘Holy Basil’in English. The chemical constituents isolated from various parts of the plant include eugenol, cardinene, cubenol, borneol, linoleic acid, linolenic acid, oleic acid, palmitric acid, steric acid, Vallinin, Vicenin, Vitexin, Vallinin acid, Orientin, Circineol, Gallic Acid, vitamin A, vitamin C, phosphorous and iron. Eugenol is a phenolic compound and major constituent of essential oils (l-hydroxy-2-methoxy-4-allylbenzene), the active constituent present in *Ocimum sanctum* L., has been found to be largely responsible for the therapeutic potentials of Tulsi. *Ocimum sanctum* has been shown to possess multifarious medicinal properties such analgesic activity, anti-ulcer activity, immunomodulatory activity, antiasthmatic

activity, anticancer activity, anticonvulsant activity, antidiabetic activity, antihyperlipidemic activity, anti-stress activity in addition to possessing useful memory enhancer and neuroprotective activity.

Tulsi has anti-inflammatory properties as it undermined vata. So, its external application on the swollen area helps to reduce swelling and pain [19-27].

The objective of the present research is to formulate and evaluate varying concentrations of curcuminoids, tulsi oil, and eucalyptus oil for the preparation of a safe, effective and stable gel.

MATERIALS AND METHODS:

Isolation of Curcuminoids: 250 g of dried *C. longa* rhizomes powder is subjected for extraction in Soxhlet extractor by using n-hexane as a solvent till complete extraction is complete. Then mark is packed into thimble and subjected for extraction by using methanol. The methanolic extract is collected and the solvent is evaporated by rotary vacuum evaporator. Then, it is dissolved in 500 mL toluene. The solution is poured into a separatory funnel. Then, 200 mL NaOH 0.2 M is added to the solution and shake for minutes. The aqueous phase is collected and acidified to pH 3 by HCl 0.2 M. The brown extract undergoes a clarification in this step and turns yellow. The filtrate is extracted with diethyl ether (3 × 250 mL). In the final extraction, the ether turns to a very pale yellow, indicating the end of the extraction. The combined ethereal phases are washed with 30 mL water and dried over $MgSO_4$. The ether is removed completely in vacuum to leave a yellow solid as crude curcuminoid products. The crude curcuminoids are purified by thin-layer chromatography. The product was chromatographed over silica gel by DCM: methanol in a ratio of 19:1 v/v. The melting point of the isolated, pure curcumin was in the range of 174-177 °C which is the same as the literature value, 176 °C [28-29].

Isolation of Volatile Oil from *Eucalyptus globulus* and *Ocimum sanctum*: Leaves of *Eucalyptus globulus* and *Ocimum sanctum* were cut, subjected to isolation of volatile oil by using Clevenger apparatus.

Formulation of Topical Gel: [30] Herbal gel was prepared using carbopol-934 as a gelling agent in 1% w/w concentration with deionized water using a mechanical stirrer. Then skin pH (6.8-7) was maintained by drop wise addition of tri-ethanolamine with continuous stirring. Various concentrations of curcuminoids either with fixed concentration of eucalyptus oil or tulsi oil or with both essential oil were added to the gel and stirred for sufficient time for homogeneous mixing. Prepared gel was filled in collapsible tubes and stored at a cool and dry place. Formulation is evaluated for following parameters.

Organoleptic Evaluation: Physical parameters such as colour, appearance were recorded.

Viscosity: Viscosity of gel was measured by using Brookfield viscometer (Brookfield viscometer RVT) with spindle number 7.

Extrudability: [31] The gel formulations were filled in standard capped collapsible aluminum tubes and sealed by crimping to the end. The weights of the tubes were recorded. The tubes were placed between two glass slides and were clamped. 500 gm was placed over the slides and then the cap was removed. The amount of the extruded gel was collected and weighed. The percent of the extruded gel was calculated (>90% extrudability: excellent, >80% extrudability: good, >70% extrudability: fair).

Spreadability: [32] Spreadability was determined by the apparatus which consists of a wooden block, which was provided by a pulley at one end. By this method spreadability was measured on the basis of slip and drag characteristics of gels. An excess of gel (about 2 g) under study was placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with a hook. A 1 kg weight was placed at the top of the two slides for 5 min to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 80 g with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm was noted. A shorter interval indicated better spreadability. Spreadability was calculated using the following formula:

$$S = M \times L / T$$

Where, S = Spreadability, M = Weight in the pan (tied to the upper slide), L = Length moved by the glass slide, T = Time (in sec.) taken to separate the upper slide from the ground slide.

Measurement of pH: [33-34] The pH of developed gel formulations was determined using digital pH meter. The measurement was performed at 1, 30, 60 and 90 days after preparation to detect any change with time. 1 gm of gel was dissolved in 100 ml distilled water and kept aside for two hours. The measurement of pH of formulation was done in triplicate and average values are calculated.

Homogeneity: [33-34] After the gels have been set in container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.

Grittiness: [35] All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under a light microscope. Hence, obviously they gel preparation fulfills the requirement of freedom from particular matter and form grittiness as desired for any topical preparation.

Stability Study: [36-37] The stability study was performed as per ICH guidelines. The formulated gel was filled in collapsible tubes and stored at different temperatures and humidity conditions, *viz.* 25 ± 2 ºC / 60 ± 5% RH, 30 ± 2 ºC / 65 ± 5% RH, 40 ± 2 ºC / 75 ± 5% RH for a period of three months and studied for appearance, pH and spreadability.

Skin Irritation Test: [38] The Wistar rats of either sex weighing 150-200 g were used for this test. The intact skin was used. The hair was removed from the rat three days before the experiment. An herbal extract containing gel was used on the test animal and gel base on the control group. The animals were treated daily up to seven days and finally, the treated skin was examined for erythema and edema.

Evaluation of Anti-Inflammatory Activity: [39-40]

Carrageenan-Induced Rat Paw Edema: Albino Wistar rats of either sex, weighing 150-200 g were used. They were housed in standard environmental conditions and fed with standard rodent diet with water *ad libitum*. All animal procedures were followed in six groups (Control, F1, F2, F3, F4 and Standard) of six animals each. Animals fasted for 24 h before the experiment with water *ad libitum*. Edema was induced by injecting 0.1 ml of 1% w/v carrageenan in saline into the plantar side of the right hind paw of rat 1 h before each experiment. 0.2 g of the herbal gel was applied to the plantar surface of the hind paw by gentle rubbing 50 times with the index finger. Rats of the control groups received the plain gel base and rats of the standard group received 0.2 g 1% diclofenac sodium gel. Drugs or placebo was applied 1h before the carrageenan injection. Paw volume was measured immediately after carrageenan injection and at 1, 2, 3 and 4 hrs intervals after the administration of the noxious agent by using an Ugo Basile Plethysmometer. The percentage of anti-inflammatory activity was calculated using the formula given below:

% inhibition = Control group mean − test group mean × 100 / control group mean

Statistical Analysis: Data are reported as the mean ± SEM (Standard Error Mean) and were analyzed statistically by means of an analysis of variance (ANOVA) followed by Student's t-test. Values of $p<0.05$ are regarded as significant.

RESULTS AND DISCUSSION: The herbal gel was prepared by using combinations of ingredients as shown in **Table 1,** and subjected to the evaluation of various parameters. All gel formulations have yellowish translucent color and have a smooth feel on an application that remained the same on the stability testing period. The measurement of the viscosity of the prepared gel was done with Brookfield Viscometer. In all these formulations, the optimum viscosity was found and results are deputed in **Table 2**. The Extrusion of the gel from the tube is important during its application and inpatient acceptance. Gels with high consistency may not extrude from tube whereas, low viscous gels may flow quickly and hence suitable consistency is required in order to extrude the gel from the tube. Extrudability of all gel formulations was found to be good and results are deputed in **Table 3**.

The pH values of all prepared formulation ranged from 6-7 which are considered acceptable to avoid the risk of irritation on application to the skin. All

formulations when prepared and after three months remain homogeneous without any gritty particle. Furthermore, the stability study's results revealed the preparation was stable under normal storage conditions. Results of the skin irritation test indicate that prepared gels were not produced irritation, redness or edema on the application and free from the dermatological reaction. Edema inhibition in carrageenan-induced rat paw edema by various formulations and standard diclofenac sodium gel was represented in **Fig. 1**. Formulation F3 and F4 have shown significant (P<0.01) anti-inflammatory activity. Formulations F3 and F4 significantly inhibited the inflammation to the extent of 26.83%, 43.90% at 3 h and 37.78%, 57.77% 4 h respectively, while the reference drug; diclofenac sodium reduced the inflammation by 60.97% at 3 h and 73.33% at 4 h.

TABLE 1: COMPOSITION OF FORMULATIONS CONTAINING VARIOUS CONCENTRATIONS OF CURCUMINOIDS

Ingredients	Quantity in percent			
	F1	F2	F3	F4
CM	0.25	0.50	0.75	1
TO	0.25	0.25	0.25	0.25
EO	0.25	0.25	0.25	0.25
Carbopol 934	1	1	1	1
Methyl Paraben (0.5%)	0.2	0.2	0.2	0.2
Propyl Paraben (0.2%)	0.1	0.1	0.1	0.1
Propylene glycol 400 (5%)	5	5	5	5
Triethanolamine	q.s.	q.s.	q.s.	q.s.

TABLE 2: EVALUATION PARAMETERS OF FORMULATIONS F1-F4

Formulation	Appearance	Viscosity	Spreadability	pH	Homogeneity	Skin irritation test
F1	Pale yellow	4120	23.91	6.4	Homogeneous	No reaction
F2	Pale yellow	4180	25.18	6.8	Homogeneous	No reaction
F3	Yellow	4290	21.34	6.7	Homogeneous	No reaction
F4	Yellow	4346	25.61	6.9	Homogeneous	No reaction

TABLE 3: EXTRUDABILITY OF F1-F4 HERBAL GEL

Formulation	Weight of formulation	Weight of gel extruded	Extradibility amount (%)	Grade
F1	10.62	9.63	90.68	Good
F2	10.36	9.12	88.03	Good
F3	10.42	9.51	91.26	Good
F4	10.91	9.18	84.14	Good

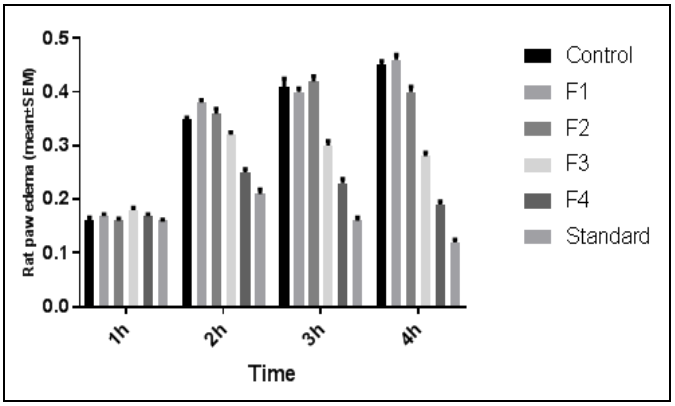

FIG. 1: ANTI-INFLAMMATORY ACTIVITY OF PLAIN GEL BASE AS CONTROL, FORMULATIONS F1, F2, F3, F4 ABD STANDARD DICLOFENAC SODIUM IN CARRAGEENAN INDUCED RAT PAW EDEMA MODEL. Each column represents a mean ± SEM of 6 animals. Statistical differences between the treated and the control groups were evaluated by ANOVA.

CONCLUSION: Results have shown that gel formulations are good in appearance, homogeneity, extrudability, and spreadability.

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CONFLICTS OF INTEREST: Nil

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