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EVALUATION OF ANTI-INFLAMMATORY ACTIVITY OF METHANOLIC EXTRACT OF COSMOS SULPHUREUS PLANT BY USING *IN VIVO* STUDIES

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Abstract:

Inflammation is a complex biological response to harmful stimuli, often associated with various chronic diseases. The present study aimed to evaluate the anti-inflammatory activity of the methanolic extract of Cosmos sulphureus seeds using in vivo models. The extract was prepared through Soxhlet extraction, and preliminary phytochemical screening revealed the presence of flavonoids, alkaloids, tannins, and phenolic compounds-known for their anti-inflammatory properties. Wistar albino rats were divided into groups and subjected to carrageenan-induced paw edema and cotton pellet-induced Dextran-Induced Paw Edema, Formaldehyde-Induced The methanolic extract was administered in graded doses (100, 200, and 400 mg/kg body weight), and its effect was compared with a standard drug (diclofenac sodium). Results showed a dose-dependent and significant ($p < 0.05$) reduction in paw edema and granuloma formation, indicating potent anti-inflammatory activity. The findings suggest that Cosmos sulphureus seed extract possesses promising anti-inflammatory potential, likely due to its phytoconstituents, and may serve as a natural alternative for managing inflammatory conditions.

Keywords: *Anti-Inflammatory, Cosmos sulphureus, Nonsteroidal, inflammation*

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1. INTRODUCTION:

Inflammation usually occurs when infectious microorganisms such as bacteria, viruses or fungi invade the body, reside in particular tissues and/or circulate in the blood [1, 2, and 3]. Inflammation may also happen in response to processes such as tissue injury, cell death, cancer, ischemia and degeneration [1, 4, 5, 6, 7, 8, and 9]. Mostly, both the innate immune response as well as the adaptive immune response are involved in the formation of inflammation [1, 5, and 9]. The innate immune system is the foremost defense mechanism against invading microorganisms and cancer cells, involving the activity of various cells including macrophages, mast cells and dendritic cells. The adaptive immune system involves the activity of more specialized cells such as B and T cells who are responsible for eradicating invading pathogens and cancer cells by producing specific receptors and antibodies.

Numerous inflammatory mediators are synthetized and secreted during inflammatory responses of different types. Inflammatory substances are usually divided to two main categories: pro- and anti-inflammatory mediators. Nevertheless, some mediators such as interleukin (IL)-12 possess both pro- and anti-inflammatory properties [10]. Among the inflammatory mediators and cellular pathways that have been extensively studied in association with human pathological conditions are cytokines (e.g., interferons, interleukins and tumor necrosis factor α), chemokines (e.g., monocyte chemoattractant protein 1), eicosanoids (e.g., prostaglandins and leukotrienes) and the potent inflammation-modulating transcription factor nuclear factor κ B.

Tumor necrosis factor (TNF)-α is an important pro-inflammatory cytokine that is secreted from various cells and exerts many cellular effects [11,12]. TNF-α has been associated with multiple illness states in humans, including immune and inflammatory diseases, cancer, psychiatric disorders, among others. Another cytokine which mostly exerts a pro-inflammatory activity is IL-1α [13, 14]. It stimulates the secretion of pro-inflammatory cytokines such as IL-1β and TNF-α [13, 14]. However, IL-1α has also been associated with anti-inflammatory activity. Similar to IL-1α, IL-6 usually acts as a pro-inflammatory cytokine but it also has some anti-inflammatory effects. As mentioned above, the IL-12 family of cytokines (including IL-12, IL-23, IL-27 and IL-35) possess both pro- and anti-inflammatory functions [10,15,16]. On the other hand, IL-10 is a potent anti-inflammatory cytokine the activity of which impedes the action of many pro-inflammatory mediators [17, 18, and 19]. By weakening and controlling the inflammatory response IL-10 helps to maintain tissue homeostasis and attenuates the damage that may result from an exaggerated inflammatory response [17, 18, and 19].

Prostaglandin (PG) E2 is probably the most studied PG in association with human physiological and pathological conditions [20]. It has various physiological roles including regulation of normal body temperature, gastric mucosal integrity, renal blood flow and the function of female reproductive system. On the other hand, alterations in PGE2 activity are associated with pathological conditions such as inflammatory diseases, abnormal changes in body temperature, colorectal cancer, among others. The pathway of PGs synthesis starts with generation of arachidonic acid from cell membrane phospholipids by phospholipase A2 (PLA2). Then, arachidonic acid is converted to PGs by the enzyme cycloogygenase (COX) [20]. Among the three known COX isoforms (COX-1, COX-2 and COX-3), the inducible enzyme COX-2 is recognized as the most active during inflammatory processes. Leukotrienes (LTs) such as LTB4 were also linked to human illness states including inflammation, asthma and depression [21,22,23]. LTs are produced by the enzyme 5-lipooxygenase (5-LOX) [22]. Another enzyme that is highly associated with inflammatory conditions is nitric oxide synthase (NOS) which produces nitric oxide (NO) [24]. Similar to COX-2, inducible NOS (iNOS) is the most pro-inflammatory NOS isoform.

The transcription factor nuclear factor κ B (NFκB) is a prominent regulator of immune and inflammatory responses and is highly involved in the pathophysiology of cancer [25,26,27]. In mammals, the NFκB machinery comprises several members (e.g., p50 and p65) which regulate both physiological and pathological processes [25,26]. At resting (un-stimulated) conditions NFκB resides in the cytoplasm [26]. Following activation by various infectious/inflammatory/mitogenic stimuli, NFκB proteins translocate to the nucleus and induce transcription of inflammatory-associated genes [26,27].

The practice of using plants, their parts or extracts as anti-inflammatory compounds is known since antiquity. For example, concentrated, viscous aqueous extract of ripe carob (Ceratonia siliqua L.) has been used for decades in Arab folk medicine, especially for treating mouth inflammations [28]. The use of plants or plant products for medicinal purposes was mostly documented in books and, lately, in an enormous number of websites (where the reliability

of some of these websites must be examined carefully). In the last decades, hundreds of research and review articles were published regarding the anti-inflammatory activities of plants. In this review we introduce some highlights of the literature published mainly during the last three decades, with a few references to earlier reports.

The role of natural products as remedies has been recognized since ancient times. There has been considerable public and scientific interest in the use of natural products to combat human diseases such as cardiovascular disease, cancer, and Inflammatory disease (which may in any case, actually include another chronic disease, like CVD, cancer, and diabetes). Despite major scientific and technological progress in combinatorial chemistry, drugs derived from natural products still make an enormous contribution to drug discovery today [29]. Inflammation, which is a pattern of response to injury, involves the accumulation of cells and exudates in irritated Tissues, which allows protection from further damage. Inflammation has been studied for thousands of years in an attempt to combat its effects on the body. In AD 30, Celsius described the 4 classic signs of inflammation (rubor, calor, dolor, and tumor, or redness, heat, pain, and swelling), and used extracts of willow leaves to relieve them. [30]. For many years, salicylate-containing plants were applied therapeutically and led to the production of a major anti-inflammatory drug - Aspirin. Aspirin, an agent with anti-inflammatory activity, is derived from natural sources and is used extensively in current clinical practice.

Many other aspirin-like drugs are now available, including the non-steroidal anti-inflammatory drugs (NSAIDs). Natural products with anti-inflammatory activity have long been used as a folk remedy for inflammatory conditions such as fevers, pain, migraine, and arthritis. As the Inflammatory basis of disease becomes clear, anti-inflammatory food and food products become of greater interest. The British Nutrition Foundation report on phytochemicals provides a useful classification for those products, namely: terpenoids, flavonoids and allied phenolic and polyphenolic compounds, and sulphur-containing compounds [31].

Inflammation

The word inflammation defined as the 'reaction of irritated and damaged tissue, which still retain vitality' while others proposed that "inflammation is a process which begins following a sublethal injury to tissue and ends with complete healing". Inflammation study dates back the first coherent description of the phenomenon, presented by Celsus, a Roman physician (about B.C. 30 to A.D. 38); enunciating four cardinal signs; rubor (redness), tumor (swelling), calor (heat) and dolor (pain). To these, Galen added fifth sign functio loesa (loss of function), that was supported by John Hunter.

Boer has laid much emphasis on the changed state of blood vessels, Haller and Spallanzane in 17th and 18th century established that the redness of the inflammed part was due to the passage of blood into tissues. Cohnheim in 1882 shared the view with Samnel, that the main feature of the reaction was an increased permeability of the vascular wall; a view which has been subsequently modified and extended. Metchnikoff put forward the theory of phagocytosis being the central phenomenon [32].

There are hundreds of significant drugs and biologically active compounds developed from the traditional medicinal plants. The antispasmodic agent, vasicin, derived from *Adhatoda vasica*, anticancer drugs such as vincristine, vinblastine and D- Tubocurarine obtained from *Catharanthus rose* [33], antibacterial constituents obtained from *Diospyros melanoxylon* [34], antimalarial drugs derived from *Sida acuta*[35], steroid and Lanc Amarone with cardiotonic properties, lantamine with antipyretic and antispasmodic properties are isolated from *L. camara* [35].

Inflammation is a major condition associated with various diseases. Rheumatoid arthritis is one of the challenging disorders associated with inflammatory condition.[36]Various molecules have been proven very effective in such condition. Drugs which are in use presently for the management of pain and inflammatory conditions are either narcotics e.g. opioids or non-narcotics e.g. salicylates and corticosteroids e.g. hydrocortisone.

All of these drugs present well known side and toxic effects. It is well documented that these non-steroidal anti-inflammatory drugs (NSAIDs) produce intestinal tract ulcers (With potential internal bleeding) in 10-30 % of long-term users, and erosions of the stomach lining and intestinal tract in 30-50 % of cases.[37]As a result of these side effects, NSAID use is associated with 10,000-20,000 deaths per year in the U.S.[38] Even the new COX-2 inhibitor drugs only been reported to reduce intestinal tract damage by 50 %, and their toxicity to the liver and kidney is still under review.[38]

Inflammation is the common underlying thread that runs through many clinical conditions; Research in

this area requires a multi-dimensional approach encompassing various fields of medical sciences, basic sciences and clinical informatics. Considering this, a two-day scientific meet on inflammation was organized in Bengaluru recently.

It brought together researchers from clinical and basic sciences working in the field of inflammation from various parts of the country. The purpose of the meet was to initiate a crosstalk on the role of inflammation in non-communicable diseases. While the meeting offered a platform for a multi-disciplinary approach to strengthening inflammation research in India, the deliberations in a nutshell are presented here.

The meet started with a talk by S. Chandrashekara (Chan Re Rheumatology and Immunology Centre and Research (CRICR), Bengaluru) on 'Dichotomy of quantifying and managing the inflammation in autoimmune disease'. He deliberated on the need 'to quantify, qualify and assess the impact' of clinical and inflammatory markers to regulate inflammation in autoimmune diseases.[40] He highlighted the dilemma faced by clinicians in deciding when to stop the inflammation and thereby the damage produced by inflammation, how much to control, and how to control the inflammatory process in autoimmune disease management by taking rheumatoid arthritis (RA) as a prototype disease. He further shared the usefulness of different lines of treatment for different forms of uveitis and scleritis patients. He cautioned about the drug-related adverse effects, the need to follow up with investigations every two weeks, and to discontinue in case of side effects in patients on therapy.

Our bodies are equipped with a built-in defence system - a complex army of infection-fighting cells and proteins that warn other cells of invaders, fight them off when they arrive, and heal any damage the resulting conflict produces. Inflammation is an important part of this defensive system, and one that is essential for our survival. You've seen the effects of inflammation in real time if you've ever gotten a paper cut, sprained your ankle, or been stung by a bee. Redness and heat, along with pain and swelling that result from an injury or infection, are evidence of the inflammatory process underway beneath the skin's surface. Not visible but similar in process is the inflammation that results when you come down with an infection like the flu or pneumonia. In both cases, the immune system is waging a battle inside your body against invading microbes. Without its defences, a minor cut or illness could quickly turn deadly.[41]

2. METHADOLOGY:

Extraction procedure

Coarsely powdered cosmos sulphureus Seeds were used for extraction with methanol by using Soxhlet method for 6-8 hours. 25g of dried powder was weighed and 250mL of solvent methanol is used for the extraction. The extracts were evaporated by using a rotary evaporator and dried at room temperature. The obtained crude extracts were weighed and stored at 4^{o}C for further analysis[42].

PHARMACOLOGICAL STUDY

Animals

Wistar albino rats of both sexes (180-220 g) were used for the study. The animals were obtained from Jeeva life sciences. All the rats were kept in standard plastic rat cages with stainless steel coverlids and wheat straw was used as bedding material. The animals were kept at the animal house of Department of Biosciences. The animals were facilitated with standard environmental condition of photoperiod (12:12 h dark: light cycle) and temperature (25 ± 2°C). They were provided with commercial rat feed and water given ad libitum. The use of these animals and the study protocols were approved by CCSEA recognized by ethical committee.[43]

ANTI-INFLAMMATORY STUDIES

Carrageenan induced rat paw edema

The results of anti-inflammatory activity of Methanol extract of ***Cosmos sulphureus*** on carrageenan induced paw edema. The lower dose i.e. CSME-400 showed inhibition at both early and late phase; though maximum inhibition was at late phase (66.99%, $P < 0.01$). The higher dose i.e. CSME-600 also showed maximum anti-inflammatory activity at late phase (41.16%) but this activity was less than that of CSM-400 at both early and late phase. The standard Diclofenac-10 showed maximum activity at early phase (45.46%, $P < 0.01$). In this model, the lower dose showed more inhibition of edema formation than standard diclofenac.[44]

cotton pellet induced paw edema

The results of changes in serum total protein and albumin levels in cotton pellet\ induced granuloma are given in Table 5.15. The total protein level increased at higher concentration ($P < 0.01$), and decreased at lower concentration of CSME, while diclofenac-10 group showed increase in total protein level as compared to control group. In standard and CSME-400 group, the albumin level was decreased as compared to control group. The results of changes in serum ACP and ALP levels in cotton pellet-induced granuloma are given in Table 16. The ACP level in both the doses of CSME was almost similar

to that of the control group. In standard group, the level of ACP was more as compared to control group. The ALP levels decreased in both the studied concentrations, and the decrease in lower concentration was more than that of the higher concentration. In contrast, the ALP level in the standard group increased.[45]

Dextran induced rat paw edema

The results of anti-inflammatory activity of methanol extract of ***Cosmos sulphureus***on dextran induced paw edema is shown in Table 5.11. In this model, a clear dose dependent inhibition of paw edema was observed at both early and late phases. The higher dose showed distinctly more inhibition than lower dose at both phases ($P < 0.05$). The anti-inflammatory activity of higher dose was more at later phase (49.46%) than early phase. The standard diclofenac showed poor anti-inflammatory activity in this model.[46]

Formaldehyde induced rat paw edema

The results of anti-inflammatory activity of methanol extract of *Cosmos sulphureus* in formaldehyde induced paw edema is shown in Table 5.13. Injection of formaldehyde subcutaneously into hind paw of rats produces localized inflammation. The administration of CSME- 400, CSME-600 and diclofenac-10 daily for 7 days successfully significantly ($F < 0.001$) inhibited edema induced by formaldehyde. CSME-400 and CSME-600 group showed maximum decrease in paw volume at 3 h ($P < 0.05$ and $P < 0.01$ respectively). Diclofenac-10 group showed decrease in paw volume at 3 h (47.40%, $P < 0.001$) and the decreased in paw volume at 48 h was almost same (43.39%, $P < 0.01$).[47]

STATISTICAL ANALYSIS

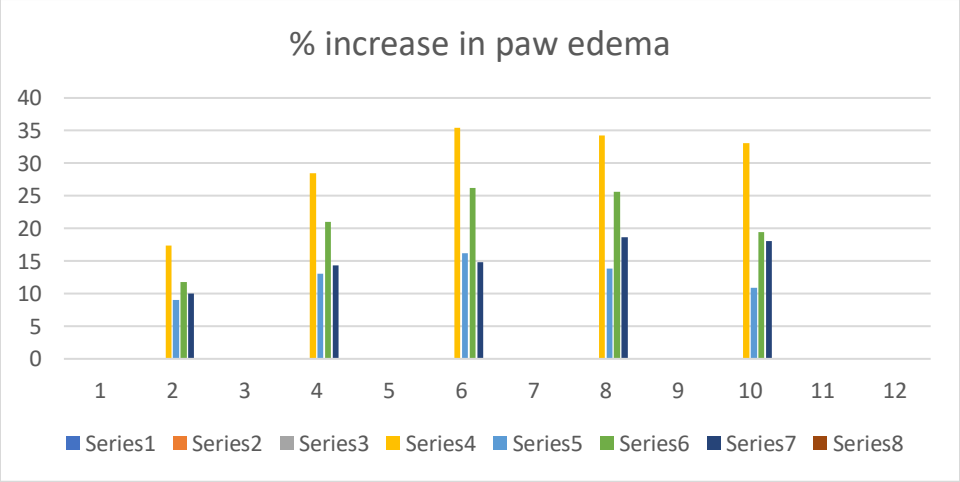
The data obtained from animal experiments are expressed as mean ± SEM (standard error of mean). For statistical analysis data were subjected to analysis of variance (ANOVA) followed by Student's t-test. Values are considered statistically significant at $F < 0.05$ for ANOVA and $P < 0.05$ for t-test.

3. Results

Table 1 Anti-inflammatory activity of methanol extract of *Cosmos sulphureus* on carrageenan induced paw edema

Treatment group	% increase in paw edema									
	After 1h		After 2h		After 3h		After 4h		After 5h	
	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change
Control	17.41±3.12		28.47±3.49		35.39±4.45		34.21±5.64		33.06±5.16	
CSME-400	9.03±1.31*	48.13↓	13.07±2.25**	54.09↓	16.18±3.09**	54.28↓	13.86±2.26**	59.48↓	10.91±2.85**	66.99↓
CSME-600	11.73±2.98	32.62↓	21.05±3.46	26.06↓	26.21±4.34	25.93↓	25.66±4.72	24.99↓	19.45±5.06	41.16↓
Diclofenac-10	10.01±1.58	42.50↓	14.33±3.86*	49.66↓	14.82±2.33**	58.12↓	18.67±3.55*	45.42↓	18.03±4.39*	45.46↓

Values are expressed as mean±SEM (n=6) *P<0.05, *P<0.01

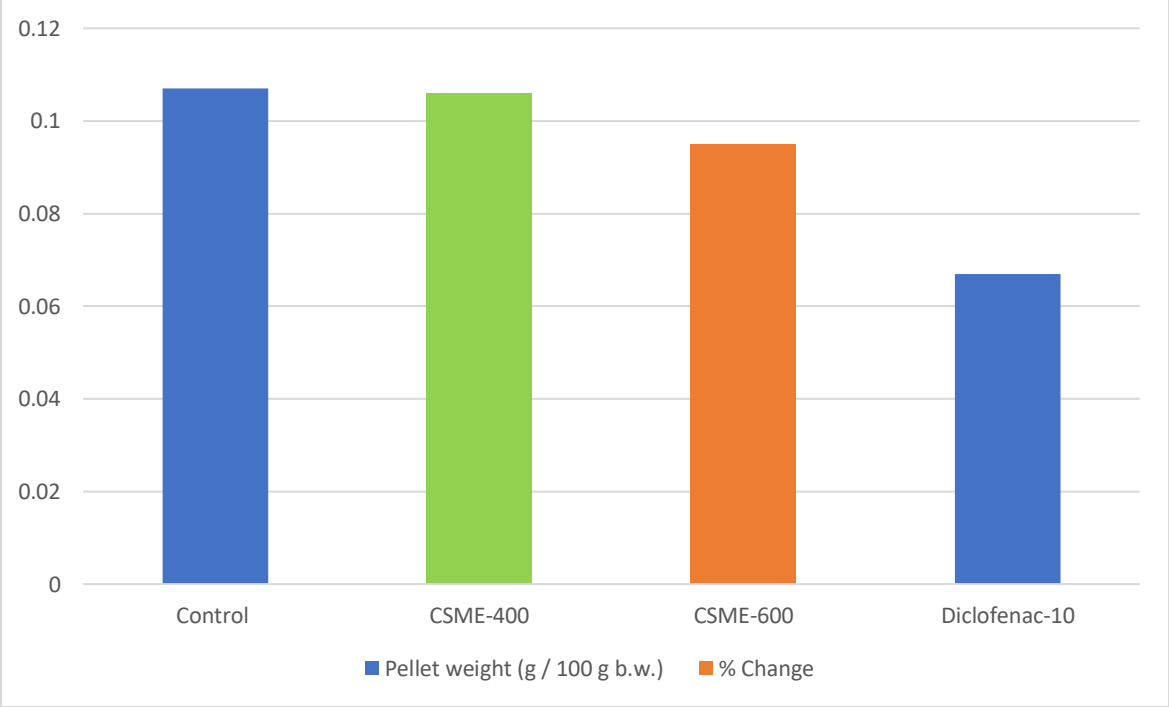


Cotton pellet induced granuloma in rats

The results of anti-inflammatory activity of methanol extract of *Cosmos Sulphureus* in cotton pellet induced granuloma is shown in Table 5.14 CSME-400 and CSME-600 groups showed 1.28% and 11.45% decrease in granuloma formation respectively as compared to control group, while standard diclofenac-10 group showed a significant decrease in granuloma formation (37.15%, $P < 0.001$).

Table 2 Anti-inflammatory activity of methanol extract of *Cosmos sulphureus* in cotton pellet-induced granuloma in rats

Treatment group	Pellet weight (g / 100 g b.w.)	% Change
Control	0.107 ± 0.005	-
CSME-400	0.106 ± 0.005	1.28↓
CSME-600	0.095 ± 0.005	11.45↓
Diclofenac-10	0.067 ± 0.004***	37.15↓



Dextran induced rat paw edema

The results of anti-inflammatory activity of Methanol extract of ***Cosmos Sulphureus*** on dextran induced paw edema is shown in Table 5.11. In this model, a clear dose dependent inhibition of paw edema was observed at both early and late phases. The higher dose showed distinctly more inhibition than lower dose at both phases ($P < 0.05$). The anti-inflammatory activity of higher dose was more at later phase (49.46%) than early phase. The standard diclofenac showed poor anti-inflammatory activity in this model.

Table: 3 Anti-inflammatory activity of methanol extract of *Cosmos sulphureus* on dextran induced paw edema.

Treatment group	dextran induced % increase in paw edema									
	After 1h		After 2h		After 3h		After 4h		After 5h	
	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change
Control	44.81±4.85		47.09±6.08		41.85±4.45		33.75±5.82		25.45±3.88	
CSME-400	33.70±3.41	25.35↓	36.47±3.56	23.04↓	30.06±5.91	28.46↓	22.44±3.01	34.53↓	20.74±3.17	19.26↓
CSME-600	27.52±3.66*	39.46↓	27.59±4.18*	42.30↓	26.95±1.59*	36.47↓	16.79±3.09*	51.78↓	12.83±3.23*	51.61↓
Diclofenac-10	42.19±4.82	5.98↓	40.04±4.60	15.29↓	36.39±4.69	13.36↓	26.61±4.68	21.80↓	23.89±3.52*	6.38↓

Values are expressed as Mean±SEM (n=6) *P<0.05, *P<0.01

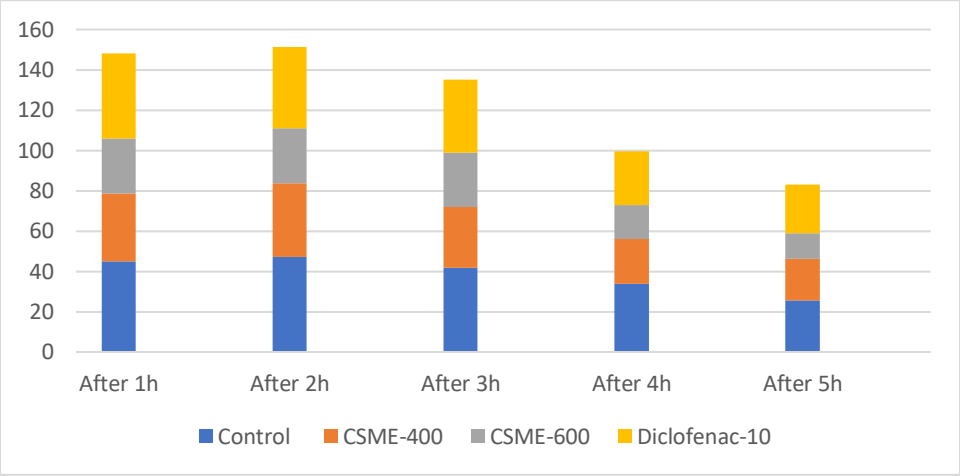
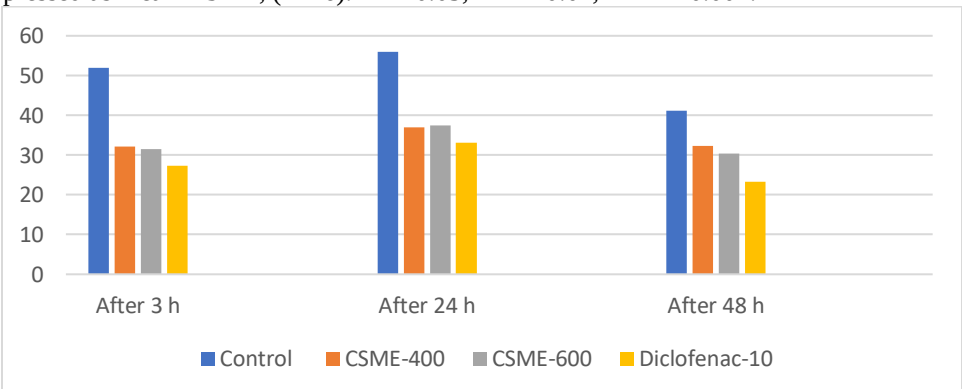


Table 4 Anti-inflammatory activity of methanol extract of *Cosmos Sulphureus* in formaldehyde induced rat paw edema

Treatment	% Increase in paw volume					
	After 3 h		After 24 h		After 48 h	
	Volume increase	% Change	Volume increase	% Change	Volume increase	% Change
Control	51.92± 3.02		55.92± 1.97		41.09± 2.23	
CSME-400	32.21± 5.23*	37.96↓	36.96 ± 2.89**	33.90↓	32.26± 5.13	21.48↓
CSME-600	31.42± 3.87**	39.48↓	37.52± 6.64*	32.90↓	30.31± 4.13*	26.23↓
Diclofenac-10	27.30±1.53***	47.40↓	33.11± 3.39**	40.79↓	23.26± 1.95**	43.39↓

Values are expressed as mean ± SEM, (n = 6). *P < 0.05; **P < 0.01; ***P < 0.001.



4. DISCUSSION:

The present study was conducted to evaluate the anti-inflammatory activity of methanolic extract of *Cosmos sulphureus* seeds (MECS) using various in vivo models including carrageenan-induced paw edema, formaldehyde-induced arthritis, dextran-induced paw edema, and cotton pellet-induced granuloma. These models simulate different phases and mechanisms of inflammation -acute, subacute, and chronic - allowing a comprehensive assessment of the extract's potential.

DEXTRAN-INDUCED PAW EDEMA (Acute Inflammation - Vascular Permeability)

Dextran-induced inflammation is largely mediated by histamine and serotonin, which increase vascular permeability. In MECS-treated groups, the extract significantly reduced edema volume compared to control, particularly in the early phase, suggesting a stabilizing effect on mast cells or histamine receptor inhibition. This indicates the presence of phytoconstituents with antihistaminic or membrane-stabilizing properties.

FORMALDEHYDE-INDUCED ARTHRITIS (Subacute/Chronic Inflammation)

This model is used to mimic chronic inflammation and rheumatoid arthritis, characterized by joint swelling, immune cell infiltration, and cartilage degradation.

MECS showed significant suppression of paw swelling on both early (inflammatory) and late (proliferative) phases of arthritis. This anti-arthritic effect may be attributed to:

- Immunomodulatory activity
- Suppression of pro-inflammatory cytokines (e.g., TNF-α, IL-1β)
- Inhibition of oxidative stress and neutrophil migration

This supports the use of MECS in chronic inflammatory conditions like rheumatoid arthritis.

COTTON PELLET-INDUCED GRANULOMA (Chronic Inflammation / Proliferative Phase)

This model evaluates granuloma formation and proliferative inflammation, including fibroblast proliferation, collagen formation, and angiogenesis. MECS-treated groups showed a significant reduction in dry weight of granuloma tissue, indicating the inhibition of proliferative components of chronic inflammation. This suggests the extract may modulate fibroblast activity and collagen deposition, possibly by downregulating growth factors and cytokines involved in tissue proliferation.

5. CONCLUSION:

The methanolic extract of *Cosmos sulphureus* seeds demonstrated significant anti-inflammatory activity in both acute and chronic in vivo models. Its effectiveness in:

- Carrageenan and dextran models suggest acute inflammation inhibition.
- Formaldehyde and cotton pellet models supports its role in chronic/proliferative inflammation.

These results justify the traditional use of *Cosmos sulphureus* in inflammation-related conditions and encourage further isolation of active constituents and mechanistic studies.

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