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PHARMACOLOGICAL EVALUATION OF SWIETENIA MACROPHYLLA SEED EXTRACT AS ANALGESIC AND ANTI-INFLAMMATORY PREOPERTIES IN MICE

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ABSTRACT:Background and objective: Several studies in analgesic and anti-inflammatory activity identifying the natural treating agents with better safety profile against synthetic drug. The current study was observed the analgesic and anti-inflammatory activities through methanolic seed extract of Swieteniamacrophylla. The present study was designed as pharmacological evaluation of Swieteniamacrophylla seed extract as analgesic and anti-inflammatory properties in mice.

Materials and Method: The pharmacological activity of Swieteniamacrophylla seed was performed at the dose of 100 mg/ kg, 200 mg/kg and Aspirin 100 mg/kg, diclofenac 10 mg/kg. The analgesic activity was resolute through; hot-plate method, tail-flick method, acetic-acid writhing response in mice, even as in anti-inflammatory activity was determined by; carrageenan-induced paw edema, xylene-induced ear edema assay, formaldehyde-induced inflammatory activity studies were performed.

Results and discussion: Methanolic seed extract of Swieteniamacrophylla showed significant analgesic and anti-inflammatory activity against disease control group. In chronic anti-inflammatory activity test and standard drug act on the cytokines mediators affect like; IL-6, IL-10 and TNF-α. Analgesic and anti-inflammatory activity of methanolic seeds extract of Swieteniamacrophylla King was determined by the comparison between test and standard drug on the basis of improvement in elevated levels of biomarkers such as; cytokines level of TNF-α, IL-6, IL-10, COX-1, COX-2 and opioid receptors. Then the methanolic seed extract of Swieteniamacrophylla (100 and 200 mg/kg) was more significance effective as compared to standard drug (Diclofenac 10 mg/kg and Aspirin 100 mg/kg) on the basis evaluation of all over biological parameter and histopathological activities.

Conclusion: Finally it was conclude that the methanolic seed extract of Swieteniamacrophylla showed excellent analgesic and anti-inflammatory activity but in chronic inflammatory activity showed 80 to 90% effect due to presence of alkaloids, tannins, phenol, terpenoids, flavonoids, carbohydrate and glycosides.

Keyword:Swieteniamacrophylla,TNF-α,IL-6,IL-10,COX-1andCOX-2.

INTRODUCTION

Non-steroidal Anti-inflammatory is medicinal drugs that are as usually completely different from the steroids drugs that are the type of medicine. Steroidal drugs obtain from synthetic drugs and naturally synthesize from human body. Steroidal drugs are widely used for reduce analgesic and inflammation activity. Steroidal drugs are long term used by patient that are cause side effects and risk like; weight gain and/or increase in appetite, stomach pains, thinning of the bones (osteoporosis), bruising easily, indigestion, a round face, stretch marks, thinning of the skin. NSAID's is extremely used for the treatment or prevent of reversible sensation of pain, inflammation and fever. The Non-steroidal Anti-inflammatory categories drugs cause wide range of side effects and risks depend on the specific drug, but largely include an increased risk of gastrointestinal ulcers and bleeds, heart attack, and kidney disease [1]. NSAID's are generally used in both chronic and acute disease condition. The intensity of analgesic and anti-inflammation activity depends on the several factors these factor like; Interleukin-1β, COX-1 (Prostaglandin), COX-2 (Cyclooxygenase), COX-3 (Isoform of COX-1),TNF-α (Tumor Necrosis Factor-α), PGE2 (Prostaglandin E2), Interleukin-6, Interleukin-8, Interleukin-10, Interleukin-4, Interleukin-2, Interleukin-33, CCL3, CXCL1, CCR5, T-

helper, 1 and 2 cytokines, and IFN-γ that are induce and inhibit pain and swelling [2].

Peripheral pathways

Nociceptors are naked nerve endings of first-order afferent neurons that have soma in dorsal root ganglions. They are distributed broadly in skin and deep tissues. Some nociceptors area unit activated by a particular style of noxious stimulus like; mechanical, thermal, or chemical whereas most of them area unit polymodal or activated by multiple sorts of noxious stimuli [4]. Nociceptors have a threshold of activation, and respond progressively according to the intensity of the stimulus to generate action potentials which are conducted in conjunction with the nerve fibers (consist of an axon) to the dorsal horn part of the spinal cord. Thinly myelinatedAδfibers (fibers of nociceptors) and unmyelinated C fibers are two types of sensory fibers (nerve fiber) conducting most of the nociceptive signals (Stimulation of Chemical, Mechanical, and Thermal sensory nerve cells) to the dorsal horn while the large myelinated Aβ fibers transmit other sensory information to the central nervous system [5]. Aδfibers are related to sharp and puncture pain, speedily conduct impulse (5-20 m/s). C fibers are related to uninteresting, burning pain and slowly conduct impulse (0.5-1 m/s). Aδfibers and C fiber are the different types of innervate skin that are supplied by a specific cutaneous nerve (associated with superficial pain) and deep somatic/visceral structures (associated with deep pain) but in different ratios. The ratio of Aδ to C fibers is 1:1 to 1:2 in cutaneous nerves, and 1:8-10 in visceral nerves [6]. A population of somatic afferent A-fibernociceptors found in the different animal like; guinea pig, mouse, rat, cat and monkey conduct impulse in the Aβ fibre conduction of velocity range. Aβ fiber is afferents role play in the transmitting of somatic nociceptive signals. Aβ fibers that are conduct signals of non-nociceptive sensory to the central nervous system may additionally have a big role in pain for circuitry planned within the gate control theory [7].

Peripheral sensitization

Under normal conditions, pain caused by an acute stimulus dissipates rapidly. Under conditions wherever the stimulus information could also be in progress, inflammatory mediators free from broken cells and hors de combat tissue will sensitize nociceptors. These sensitized nociceptors evoke a stronger response to any given stimulus than in normal state and their thresholds may be reduced such that even innocuous stimuli can activate them. Additionally silent nociceptors, which are not activated in normal state, now respond to noxious stimuli. Hence these processes collectively term result in the two clinically relevant conditions of hyperalgesia and allodynia [8].

CHRONIC INFLAMMATION

Chronic inflammation outlined as prolonged inflammatory response that involves a modification within the style of cells nearby at the location of inflammation. Chronic inflammation is that the identified by simultaneous damage and repair of tissue from inflammatory method. The characteristics feature of chronic inflammation is caused by; lymphocytes, plasma cells and macrophages, granulation tissue formation, and in specific things as; granulomatous inflammation. In some, instances the expression sub acute inflammation is working for the state of inflammation involved in both acute and chronic [20]. There are different mediators used for different effect show in the table 5.

CHEMICAL MEDIATORS OF INFLAMMATION (Harsh Mohan seventh edition 2015)

1.10.1 Vasoactive Amines: There are two significant biological activities of amines that have responsibility at intervals the first inflammatory response (First one hour) are histamine and 5-hydroxytryptamine (5-HT) or serotonin; an additionally added group of neuropeptides.

i. Histamines: It is stored in the mastocyte or labrocyte of granules, basophiles (type of WBC) and thrombocytes (Platelets). Histamine is released from these cells by various agents as under;

a) Stimulus substances causation acute inflammation that is; Heat, Cold, Irradiation, Trauma, Irritant chemicals and Immunological reactions etc.

b) Histamine concerned within the inflammatory response that's histamine-releasing factors from Neutrocytes, Monocytes (part of leukocyte) and thrombocytes.

c) Interleukins.

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The main actions of histamine are; Dilatation of blood vessels, vascular permeability, itching (fibromyalgia) and pain. Immunoglobulin E (IgE) primed mast cell and basophiles (type of WBC) also release products of arachidonic acid metabolism causation the discharge of show reacting substances of serious allergic reaction (Anaphylaxis) accommodates numerous leukotrienes like; Leukotrienes C4, Leukotrienes D4 and Leukotrienes E4 (Eicosanoids inflammatory mediators).

5-Hydroxytryptamine (5-HT or Serotonin): It is present in tissue of enterochromaffin cell-like; Spleen, Nervous system, Mastocyte or Labrocyte and Thrombocytes. The action of 5-HT (5- Hydroxytryptamine) are the same as histamine however it'sa less potent mediator of increased vascular permeability and vasodilatation than histamine.

Neuropeptides: Another category of vasoactive amines (Histamine and Serotonin) is tachykinin neuropeptides like; Substance P, Neurokinin A (Substance K), Vasoactive intestinal polypeptide and Somatostatin receptors. These small peptides are created within the central nervous system. The major proinflammatory actions of those neuropeptides are as follows;

a) Increased vascular permeability

b) Transmission of pain stimuli

c) Mast cell degranulation

Arachidonic acid metabolites: That is most significant inflammation mediators, for more than oxygen free radicals. Arachidonic acid is a polyunsaturated fatty acid, eicosatetraenoic acid (ω-6 fatty acid). Arachidonic acid is a constituent and fatty acid of the phospholipids plasma membrane; in addition some constituent and fatty acid are present in the diet. Arachidonic acid is delivering from the plasma membrane by phospholipases lipid [21]. Phospholipases lipid activated form arachidonic acid metabolites by following two pathways given in the fig. 5.

SWIETENIA MACROPHYLLA PLANT

INTRODUCTION: Swieteniamacrophylla King belonging to family Maliaceae was commonly known as Mahogany is a slow-growing, tall, tropical tree reaching at height of up to 35 to 40 meters. The trunk is enclosed with gray along with fractured bark and the crown is large, open, and rounded [22]. Whereas the pole is straight, cylindrical, buttress, and can be up to 120 cm in diameter [23]. Swieteniamacrophylla king plant is extensively distributed in the different countries like; Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela and Exotic distributed in Fiji, Haiti, India, Jamaica, Malaysia, Nigeria, Philippines, Puerto Rico, Sierra Leone, Solomon Islands, Sri Lanka, Tobago, and Trinidad [24,25]. This review was intended to the investigating of Swieteniamacrophylla king plant for its nutritious value and traditionally used in the treatment of different disease in the human being [26]. Swieteniamacrophylla king plant is extensively distributed in the different countries like; Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela and Exotic distributed in Fiji, Haiti, India, Jamaica, Malaysia, Nigeria, Philippines, Puerto Rico, Sierra Leone, Solomon Islands, Sri Lanka, Tobago, and Trinidad [24,25]. This review was intended to the investigating of Swieteniamacrophylla king plant for its nutritious value and traditionally used in the treatment of different disease in the human being [26]. The anti-microbial activities of Swieteniamacrophylla king plant in various crude methanolic extract of seed, leaves, bark, and central-fruit-axis were extensively reported the activity in different journal. The anti-microbial activity of the Swieteniamacrophylla king leaf, seed and central fruit-axis extract was evaluated against gram-positive, gram-negative bacteria and funguses established on the zone of inhibition using healthy disk diffusion assay method [27,28].The crude extracts of Swieteniamacrophylla were subjected to various phytochemical screening tests. The phytochemical tests exhibited the presences of common phytocompounds such as; alkaloids, flavonoids, tannins, terpenoids, glycosides, saponin, volatile oils, amino acids, and proteins as major active constituents [29,30]. The seed extract had the significant level of inhibitory effects on the growth of bacteria viz., Staphylococcus aureus, E. coli, and fungi viz., Fusariumsp, Helminthosporiumsp, and Alternaria sp. The anti-microbial activity exhibited a linear relationship with extract

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concentrations. The Swieteniamacrophylla king seed extracts well-tried as potential activity against fungous growth [31].

Botanical Description

Synonyms: SwieteniabelizensisLundell, SwieteniacandolleiPittier, Swieteniakrukovii Gleason, Swieteniamacrophylla King, SwieteniatessmanniiHarms.

Botanical name: Swieteniamacrophylla King, Family-Meliaceae& Subfamily-Swietenoideae.Swieteniamacrophylla King Plant are different kinds of chemical constituents are according in sort of medical conditions. The bark is used to cure diarrhea and fever; crushed fruit shells are used as a potting medium. The bark produces gums and used for dyeing and tanning leather. Seed kernels yield the oil which is very bitter and purgative [32-34]. The wood is valued for high-quality wood work and furniture, musical instruments, veneer etc.

PHARMACOLOGICAL PROPERTIES

Swieteniamacrophylla king plant fruit and seeds of are process good pharmacological properties for the human health and can be exposed by testing of fruit, seeds, and leave the different chemical substances are show the health effects of reported from fruit, seeds and leaves contain. There are different main active ingredients are reported for beneficial effect of flavonoids, saponin, and alkaloids. Flavonoids are a phenolics compound that is contains lots of pigments of the plant. Flavonoids are valuable for human particularly because it is an antioxidant that exterminates free radicals and improves the immune system. The flavonoids contain anti-oxidizing properties into fruit, seeds and leave manufacture desirable effects within the aggressive various diseases caused by directly or indirectly through hypertension and heart difficulty due to oxidation. Flavonoids is reported from the enhance circulatory system by smoothing blood circulation, clearing blood vessels from clogging cholesterol, and preventing from hardening of the arteries.

MATERIALS AND METHODS

Instrument and Apparatus: Rotatory evaporator apparatus used for extraction

Preparation of extract: Swieteniamacrophylla seed was prepared by equal proportion of methanolic extract of selected plants (250gm) by using cold maceration method. The collected extract was epovarator at temperature of 25°C± 5°C. The obtained dried extract powder was stored in a well tightly closed container.

Method: Cold Maceration process

Process: Swieteniamacrophylla King seeds are collected and total weight (250 gm) then removed bark from seed. Swieteniamacrophylla King peeled seed are obtained from after removal of seed extract total weight (159 gm). Then the dried the peeled seed 45°C at hot air oven for 2 hours. Then the after dried peeled seed of Swieteniamacrophylla King crushed through mortar and pestle into small particle. Crushed powder is mixed with the methanol (450 ml) in the 1 Liter beaker. This process is also known as methanolic seed extract process. This methanolic extract process is shacked during 2 hours and beaker is covered with aluminum coil. After 3 days methanolic extract of Swieteniamacrophylla King seeds are filtered marc are removed. Then the methanolic extract of Swieteniamacrophylla King dried at room temperature.

Phytochemical Screening of Swieteniamacrophylla seed extracts

Test for alkaloids

Mayer's reagent test: 2ml of Swieteniamacrophylla seed extract was added into 2ml of concentrated HCl was added then mixed with few drops of Mayer's reagent. After few minute green color or white precipitate obtain.

Test for Tannins

FeCl3 test: 0.5ml of Swieteniamacrophylla seed extract was added into 10 ml of distilled water then mixed with few drops of ferric chloride (FeCl3) solution then immediate visible green precipitate obtains.

Test for Steroids

Liebermann-Burchard test: 1ml of Swieteniamacrophylla seed extract was dissolved with 1ml of CHCL3 then mixed with 2-3ml of acetic anhydride and two drops of concentrated H2SO4 and observed for blue green or dark green color.

H2SO4 test: To 1ml of Swieteniamacrophylla seed extract dissolved with 6-7 drops of concentrated H2SO4 and red color obtained.

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Test for saponins

Froth test: 2ml of Swieteniamacrophylla seed extract are taken in the test tube and shaken vigorously and observed for froth formation.

Test for Flavonoids

NaOH test: 3ml of Swieteniamacrophylla seed extract was dissolve in 1ml of 10% aqueous solution of NaOH then mixed with dilute HCl and obtain the yellow color precipitate.

H2SO4 test: 1ml of Swieteniamacrophylla seed extract mixed with few drops of concentrated H2SO4 then the formation of yellow color precipitate.

Test for terpenoids

Salkowaski test: 1ml of Swieteniamacrophylla seed extract was dissolve in 2ml of CHCL3 then mixed with 3ml of concentrated H2SO4 and formation of reddish brown color.

Test for glycosides

FeCl3 test: 2.5ml of Swieteniamacrophylla seed extract was mixed with 5ml of concentrated H2SO4 and boiled on water bath for 15 minutes. Then the mixture was cooled and neutralized with 20% potassium hydroxide (KOH) then added the three drops of FeCl3. After 30 minutes FeCl3 test was indicate the green to black precipitates.

Test for Carbohydrates

Molisch's Test: 1ml of Swieteniamacrophylla seed extract was mixed with 2-3 drops of Molisch's reagent (10% of 1-napthol in ethanol) and add the 1-2 ml of concentrated H2SO4 and the observed the formation of reddish violet ring at the junction.

Anthraquinones: 1 ml of Swieteniamacrophylla seed extract and mixed with few drops of 10% antacid. Then obtain the appearance of pink shading hurry shows the closeness of anthraquinone.

Test for Phenol

FeCl3 test: 2-3ml of Swieteniamacrophylla seed extract was mixed with few drops of 10% aqueous FeCl3 and obtain the blue green color precipitate.

MODELS FOR ACUTE ANALGESICS ACTIVITY

Acetic acid-induced writhing response

Twenty four (24) Swiss Albino mice of equally sexes randomly divided into four groups contain six mice each group, Swiss Albino mice are fasted for 12 hours with adequate clean water provided. The Swiss Albino mice are treated with as follows: Group I Test Drug (Swieteniamacrophylla) 100 mg/kg, Group II Test Drug (Swieteniamacrophylla) 200 mg/kg, Group III Standard drug (Aspirin) 100 mg/kg. After 60 minutes later, 0.6% of acetic acid (10 ml/kg) solution was administrating the acetic acid intraperitoneal to the all group's animals. The number of writhes (abdominal constrictions) was counted of mice after acetic-acid injection and duration of time between 5 and 20 min.

Tail-flick method

Twenty four (24) Swiss albino mice were randomly divided into three groups with four mice each group, all fasted for 12 hours with clean drinking water provided. Group I mice were pre-treated after 60 minutes before tail-flick method with 0.9% (Normal Saline); Group II Test Drug (Swieteniamacrophylla) 100 mg/kg, Group III Test Drug (Swieteniamacrophylla) 200 mg/kg, acetylsalicylate acid (aspirin) for Group IV (Standard Drug) 100 mg/kg. Then about 2-3 cm of the tail of each of the mice was placed on the heat coil pass fresh water for maintained the temperature at 50°C±1°C and room temperature at 15°C pain reaction time (PRT) the time taken for the mice to tail-flick method withdraw it from the heat coil known as the was recorded for all the mice. The cut off time was put at 15 seconds.

Hot-Plate Method

Twenty four (24) Swiss Albino mice of both sexes randomly divided into four groups contain six mice each group, Swiss Albino mice are fasted for 12 hours with adequate clean water provided. The Swiss Albino mice were then treated with as follows: Group I received 0.9% (Normal Saline), Group II Test Drug (Swieteniamacrophylla) 100 mg/kg, Group III Test Drug (Swieteniamacrophylla) 200 mg/kg, Group IV Standard drug (Aspirin) 100 mg/kg. Each of the Swiss Albino mice was placed on a hot plate maintained at the temperature of (55±1°C) and room temperature 15°C the pain reaction time (PRT) or latency period determined with a stop watch was recorded which represents the time taken for the Swiss Albino mice to react to the pain stimulus. The response to pain

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stimulus considered included; jumping, raising and licking of hind foot. The cut off time was fixed for 20 seconds.

MODELS FOR ACUTE ANTI-INFLAMMATORY ACTIVITY

4.8.1 Carrageenan -induced paw edema

Twenty four (24) Swiss Albino mice of both sexes randomly divided into four groups contain six mice each group, Swiss Albino mice are fasted for 12 hours with adequate clean water provided. The effect of oral and intraperitoneal administration of Group I Normal Saline 0.9% ml/kg, Group II Test Drug (Swieteniamacrophylla) 100 mg/kg, Group III Test Drug (Swieteniamacrophylla) 200 mg/kg, and Group IV Standard Drug (Diclofenac sodium) 10 mg/kg, after 30 min on the Carrageenan-induced paw edema by sub plantar injection of 100 µl (0.1 ml) Carrageenan (1% w/v). Inflammation was caused by carrageenan injected on foot was measured at 0, 1, 2, 3, 4 and 5 hours using digital Verniercalipers (mm).

Xylene-induced ear edema

Twenty four (24) Swiss Albino mice of both sexes randomly divided into four groups contain six mice each group, Swiss Albino mice are fasted for 12 hours with adequate clean water provided. 2% of xylene was dissolved in acetone (0.02 ml/ear) was applied to anterior and posterior surfaces of left ear of the mice. After thirty min Group I; Normal Saline 0.9% ml/kg, Group II; Swieteniamacrophylla seed extract 100 mg/kg, Group III; Swieteniamacrophylla 200 mg/kg, and Group IV Test drug; Diclofenac sodium 10mg/kg. The ear thicknesses were measured using through digital verniercalipers (mm) before and at 0, 1, 2, 3 and 4h after treatment of xylene-induced ear edema.

MODELS FOR CHRONIC ANTI-INFLAMMATORY ACTIVITY

Formaldehyde-induced inflammatory Activity

Thirty (30) Swiss Albino mice of both sexes randomly divided into three groups contain six mice each group, Swiss Albino mice are fasted for 12 hours with adequate clean water provided. Inflammation was induced by injecting 0.1 mL of 2.0% formaldehyde solution into the right hind paw, and this procedure was repeated on three days. After four days dose was administered in Swiss Albino mice as Group I Control Group: (0.9% Normal Saline), Group II Disease Group: Formaldehyde 0.1 ml, Group III Test drugs: Swieteniamacrophylla seed extract (100 mg/kg), Group IV Test Drug: Swieteniamacrophylla 200 mg/kg, Group V Test Drug: Diclofenac Sodium 10 mg/kg. The diameter of the paw and that of the right ankle were measured on day one, before the induction of the damage, and after seven days on treatment. Measurements of right and left hind paw by digital verniercalipers (mm) were done after 2, 4 and 6 h after administration of dose.

ACUTE ANALGESIC ACTIVITY

Hot-plate method

Table 10: Effect of SMSE as analgesic activity on mice using Hot-plate method.

Groups	Hot-plate method reading (sec) at different time intervals (Min)				
	0 Min	**30 Min**	**60 Min**	**90 Min**	**120 Min**
NC	5.00 ± 1.21^{NS}	4.17 ± 1.11^{NS}	4.67 ± 1.30^{NS}	4.50 ± 0.80^{NS}	4.83 ± 0.72^{NS}
SMSE 100	4.50 ± 0.80^{NS}	$4.83\pm1.11^{*}$	$7.67\pm0.49^{**}$	$8.83\pm0.94^{***}$	$4.83\pm1.53^{**}$
SMSE 200	4.00 ± 1.60^{NS}	$5.67\pm1.30^{**}$	$12.50\pm1.78^{***}$	$4.33\pm0.98^{**}$	$3.67\pm0.78^{*}$

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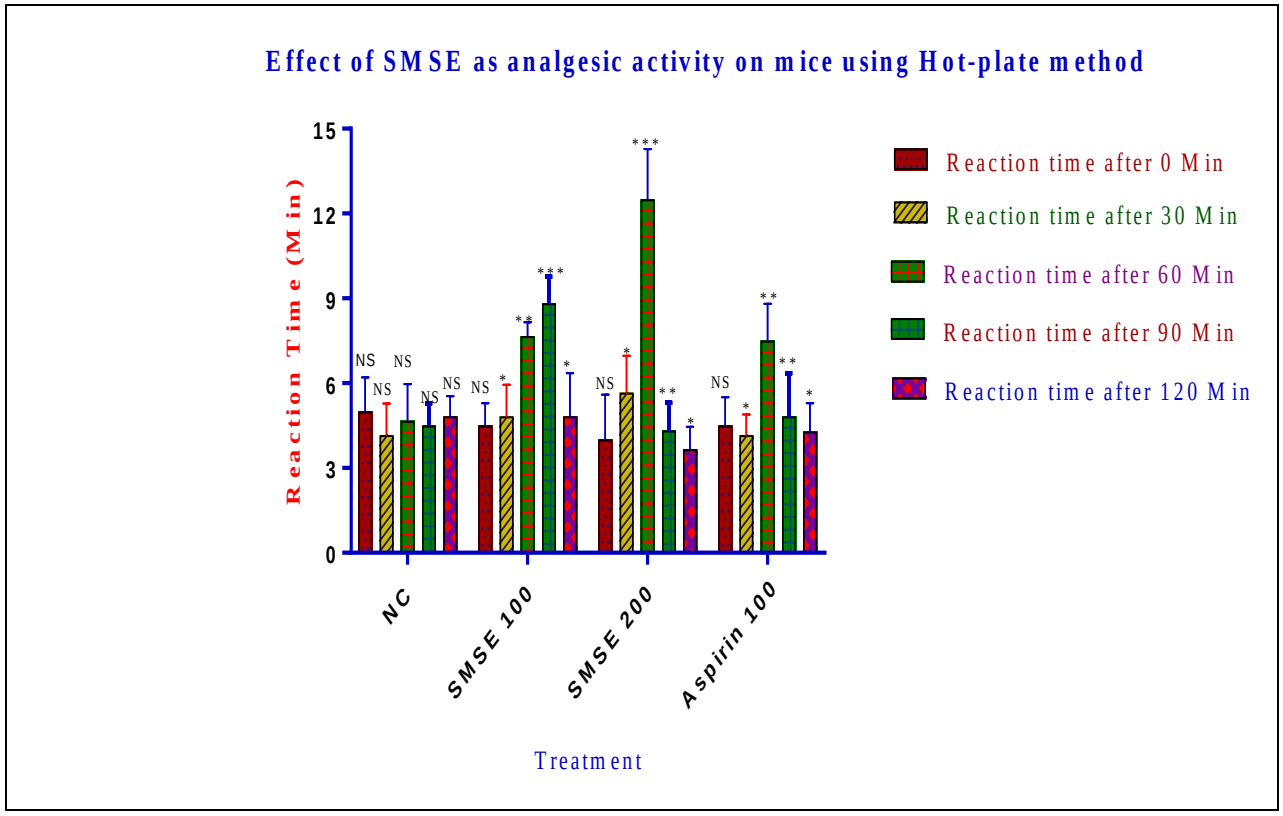
Aspirin 100	4.50±1.00^{NS}	4.17±0.72*	7.50±1.31**	4.83±1.53**	4.30±1.00*

Graph 1: Estimation of SMSE as analgesic activity on mice using Hot-plate method on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, *P<0.0001 represents statistical significance against control group, **P<0.0003 represents statistical significance against control group, ***P<0.0005 represents statistical significance against control group.

Tail-Flick method

Table 11: Effect of SMSE as analgesic activity on mice using Tail-Flick method

Groups	Tail-flick method reading (sec) at different time intervals (Min)				
	0 Min	30 Min	60 Min	90 Min	120 Min
NC	4.33±1.15^{NS}	4.17±1.11^{NS}	4.50±1.00^{NS}	4.33±1.15^{NS}	4.00±1.21^{NS}
SMSE 100	5.50±1.00^{NS}	8.67±0.98*	9.83±1.75**	10.33±1.44***	4.83±1.11*

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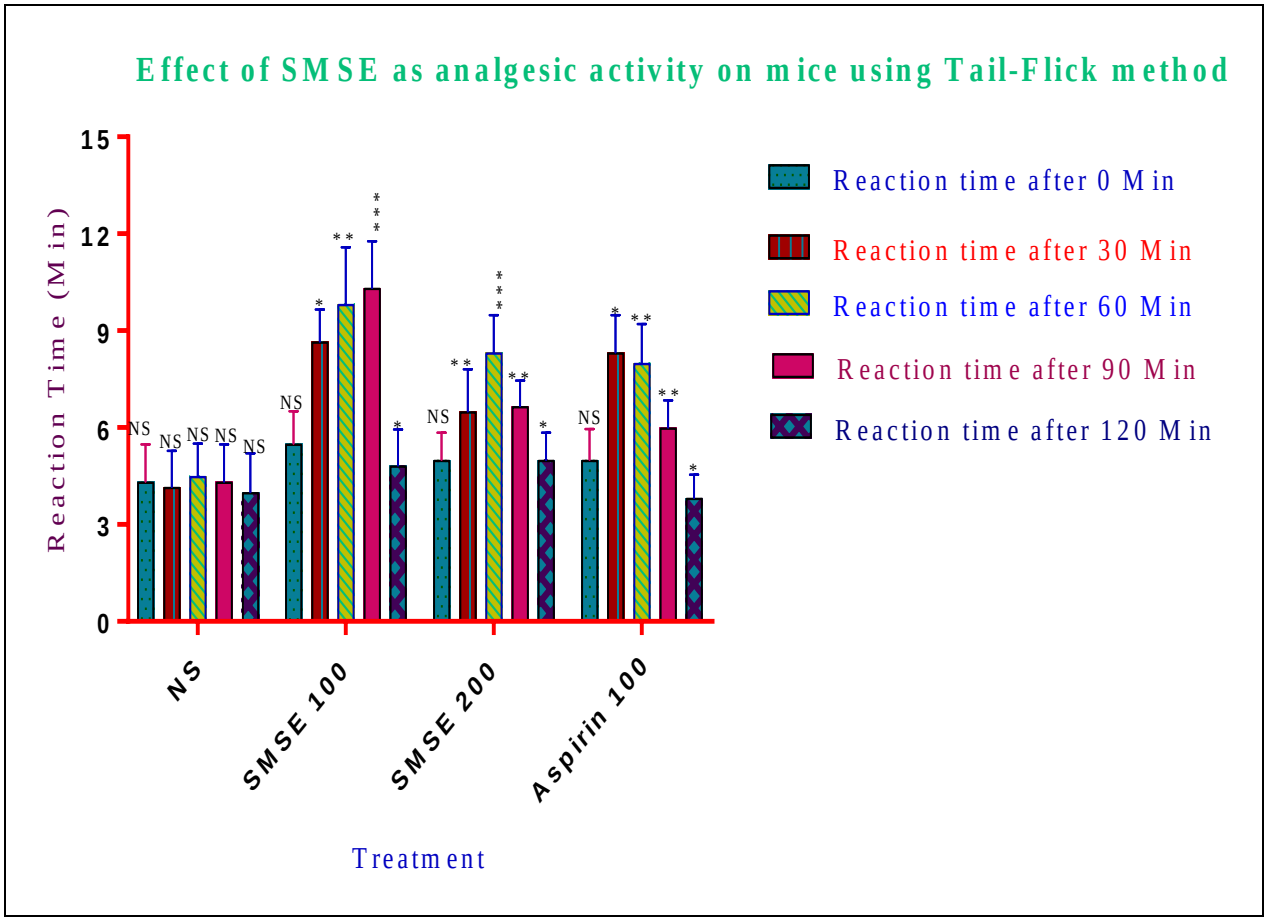
SMSE 200	5.00±0.85^{NS}	6.50±1.31*	8.33±1.15***	6.67±0.78**	5.00±0.85*
Aspirin 100	5.00±0.95^{NS}	6.33±1.44*	8.00±1.21**	6.00±0.85**	3.83±0.72*

Graph 2: Estimation of SMSE as analgesic activity on mice using Tail-Flick method on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, *P<0.0001 represents statistical significance against control group, **P<0.0003 represents statistical significance against control group, ***P<0.0005 represents statistical significance against control group.

Acetic-acid induced writhing response

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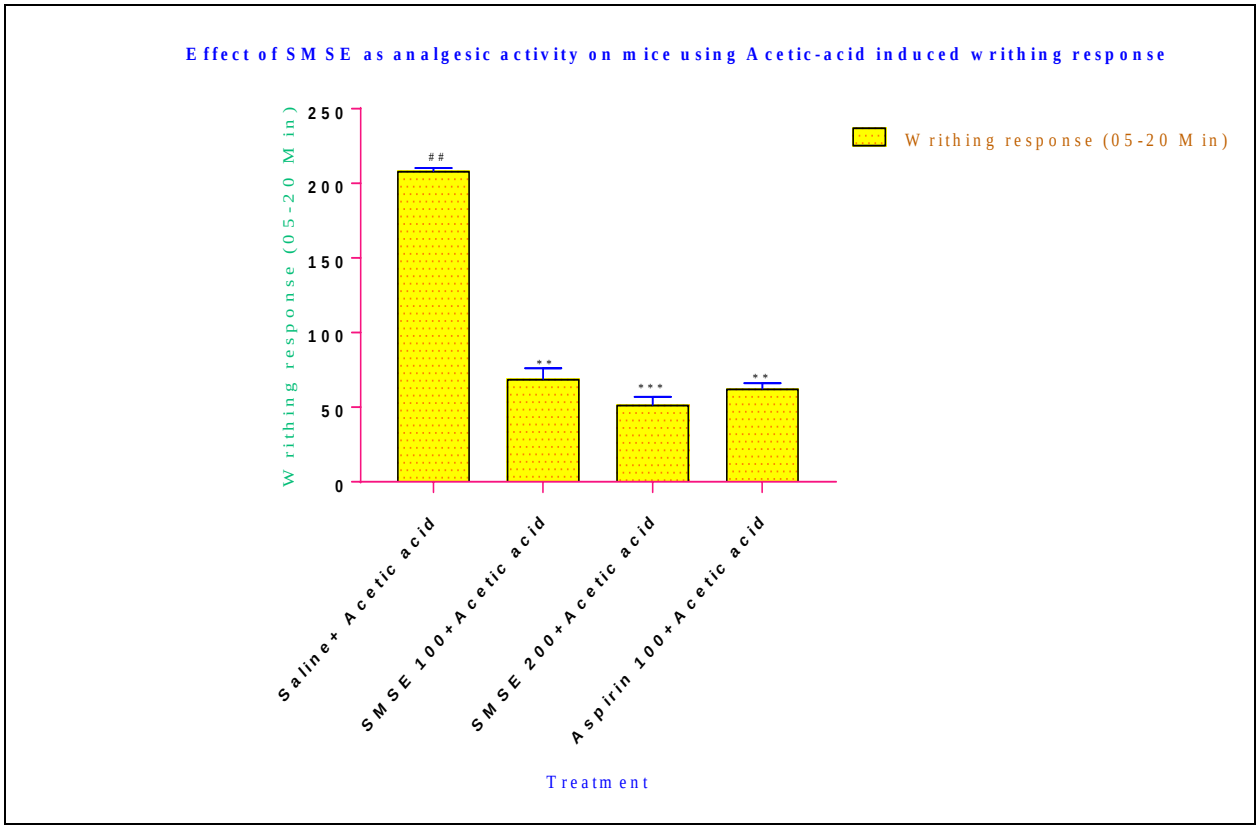
Table 12: Effect of SMSE as analgesic activity on mice using Acetic-acid induced writhing response

Treatment Groups	Writhing reading (times) at different time intervals (Min)
	Response time (05-20 Min)
Saline+Acetic acid	208.50±1.78##
SMSE 100+Acetic acid	69.13±07.07**
SMSE 200+Acetic acid	51.83±05.21***
Aspirin 100+Acetic acid	62.67±03.56**

Graph 3: Estimation of SMSE as analgesic activity on mice using Acetic-acid induced writhing response on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), ##P<0.05 represents statistical significance against control and acetic acid, **P<0.0003 represents statistical significance against normal saline and acetic acid, ***P<0.0005 represents statistical significance against normal saline and acetic acid.

ACUTE ANTI-INFLAMMATORY ACTIVITY

Carrageenan-induced paw edema

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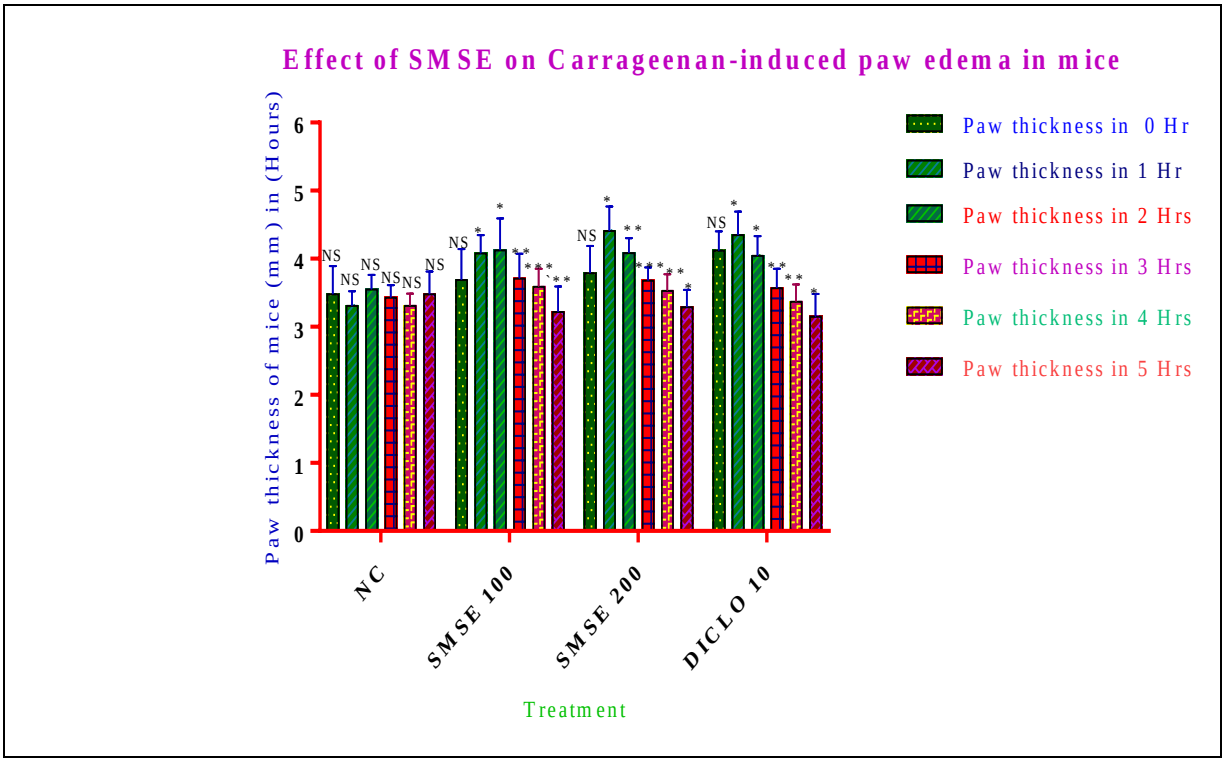
Table 13: Effect of SMSE as anti-inflammatory activity on mice using Carrageenan-induced paw edema

Groups	Paw edema reading (mm) at different time intervals (Hours)					
	0 Hours	1 Hours	2 Hours	3 Hours	4 Hours	5 Hours
NC	3.49 ± 0.40^{NS}	3.32 ± 0.28^{NS}	3.56 ± 0.20^{NS}	3.44 ± 0.17^{NS}	3.32 ± 0.17^{NS}	3.49 ± 0.32^{NS}
SMSE 100	3.70 ± 0.44^{NS}	$4.09\pm0.26^{*}$	$4.14\pm0.45^{*}$	$3.72\pm0.35^{**}$	$3.60\pm0.25^{***}$	$3.23\pm0.36^{**}$
SMSE 200	3.85 ± 0.39^{NS}	$4.42\pm0.35^{*}$	$4.10\pm0.20^{**}$	$3.69\pm0.18^{***}$	$3.54\pm0.23^{**}$	$3.30\pm0.24^{*}$
DICLO 10	4.13 ± 0.27^{NS}	$4.36\pm0.33^{*}$	$4.06\pm0.27^{**}$	$3.58\pm0.27^{**}$	$3.38\pm0.24^{*}$	$3.16\pm0.32^{*}$

Graph 4: Estimation of SMSE as anti-inflammatory activity on mice using Carrageenan-induced paw edema on different values is given as Mean±SEM of experimental animals (n=6)



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, *P<0.0001 represents statistical significance against control group, **P<0.0003 represents statistical significance against control group, ***P<0.0005 represents statistical significance against control group.

Xylene-induced ear edema assay

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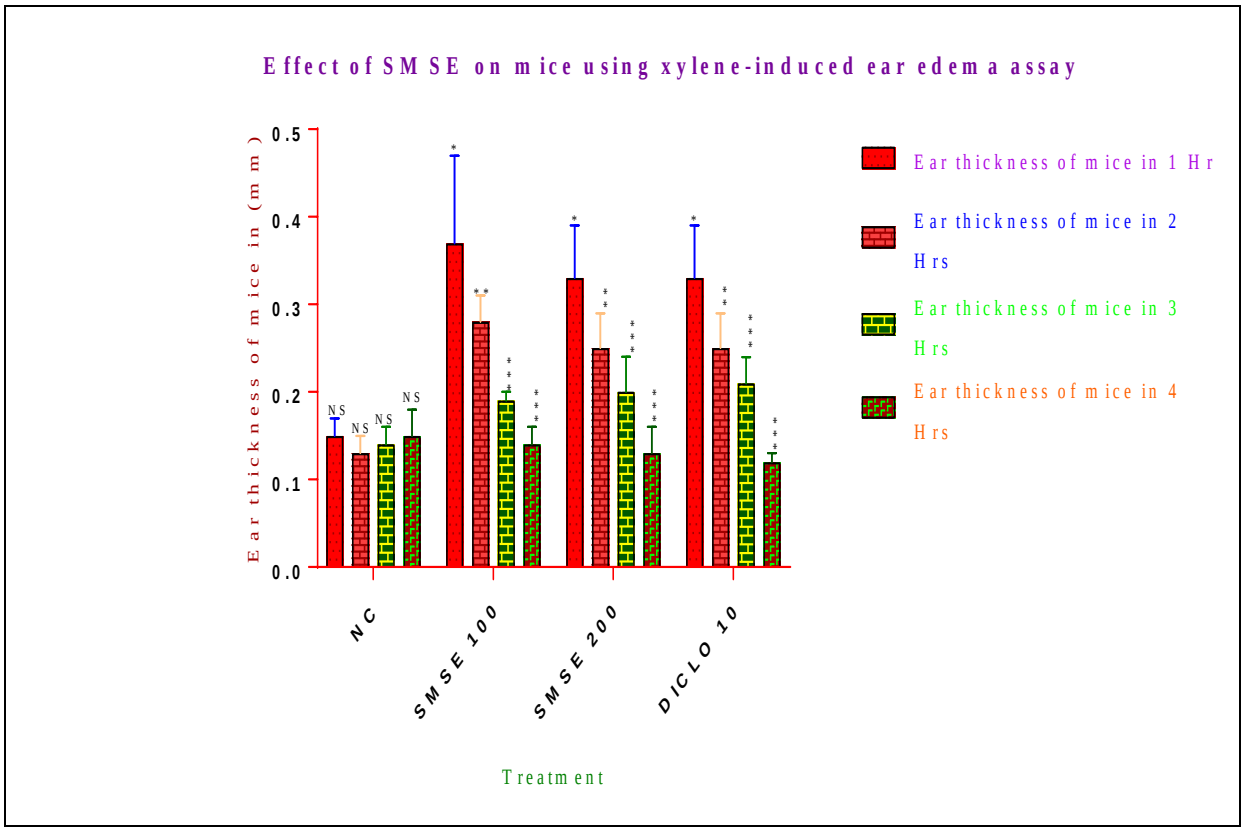
Table 14: Effect of SMSE as anti-inflammatory activity on mice using Xylene-induced ear edema assay

Groups	Ear edema reading (mm) at different time intervals (Hours)			
	1 Hr	2 Hrs	3 Hrs	4 Hrs
NC	0.15 ± 0.02^{NS}	0.13 ± 0.02^{NS}	0.14 ± 0.02^{NS}	0.15 ± 0.03^{NS}
SMSE 100	$0.37\pm0.10^{*}$	$0.28\pm0.03^{*}$	$0.19\pm0.01^{**}$	$0.14\pm0.02^{***}$
SMSE 200	$0.33\pm0.06^{*}$	$0.25\pm0.04^{**}$	$0.17\pm0.04^{***}$	$0.16\pm0.03^{**}$
DICLO 10	$0.34\pm0.06^{*}$	$0.26\pm0.04^{**}$	$0.21\pm0.03^{**}$	$0.15\pm0.01^{***}$

Graph 5: Estimation of SMSE as anti-inflammatory activity on mice using Xylene-induced ear edema assay on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, *P<0.0001 represents statistical significance against control group, **P<0.0003 represents statistical significance against control group, ***P<0.0005 represents statistical significance against control group.

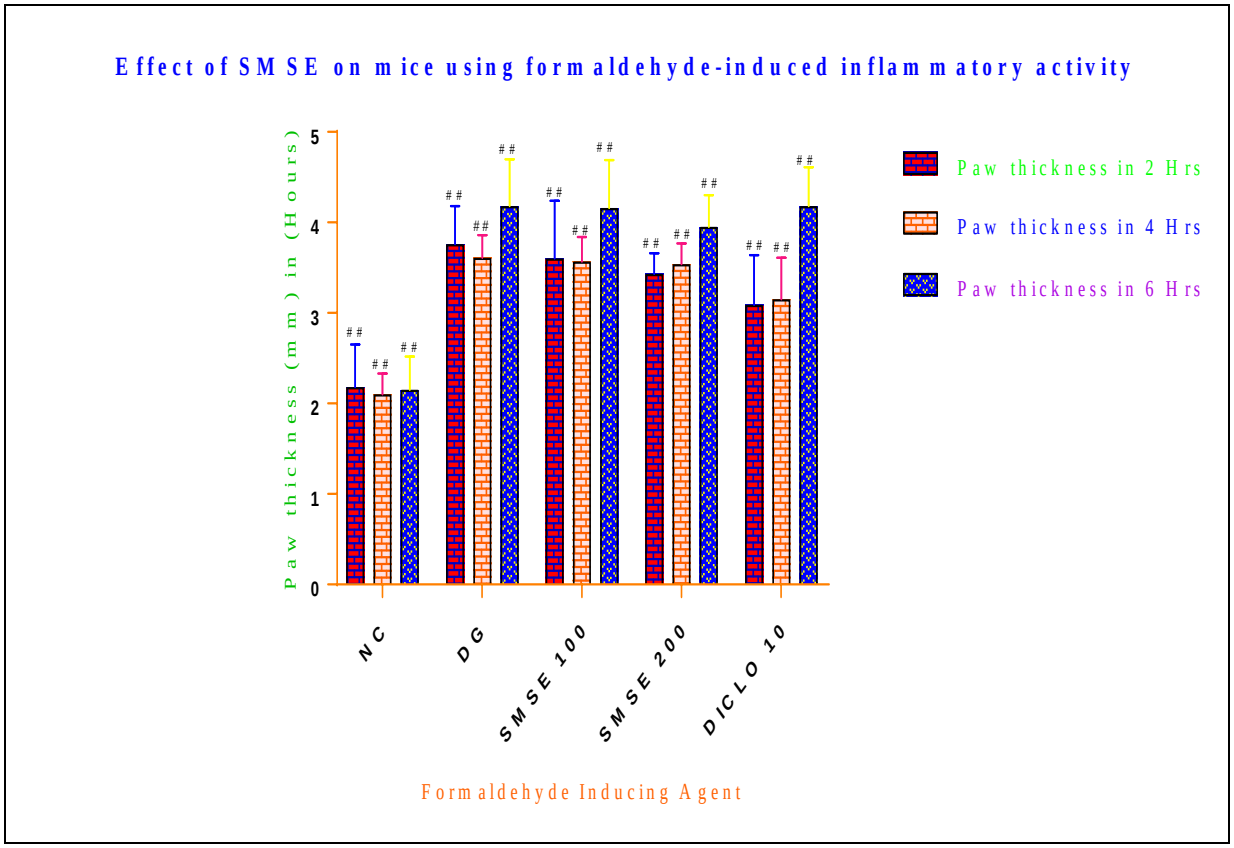
CHRONIC INFLAMMATION ACTIVITY

FORMALDEHYDE-INDUCED INFLAMMATORY FIRST DAY INDUCING AGENT

Table 15: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.18 ± 0.47^{NS}	2.10 ± 0.23^{NS}	2.15 ± 0.37^{NS}
DG	$3.76\pm0.42^{\#\#}$	$3.61\pm0.25^{\#\#}$	$4.18\pm0.52^{\#\#}$
SMSE 100	$3.60\pm0.64^{\#\#}$	$3.57\pm0.27^{\#\#}$	$4.16\pm0.53^{\#\#}$
SMSE 200	$3.43\pm0.23^{\#\#}$	$3.54\pm0.23^{\#\#}$	$3.95\pm0.35^{\#\#}$
DICLO 10	$3.09\pm0.55^{\#\#}$	$3.15\pm0.46^{\#\#}$	$4.18\pm0.43^{\#\#}$

Graph 5.6.1.1.1 Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values are given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents statistical significance against control group.

SECOND DAY INDUCING AGENT

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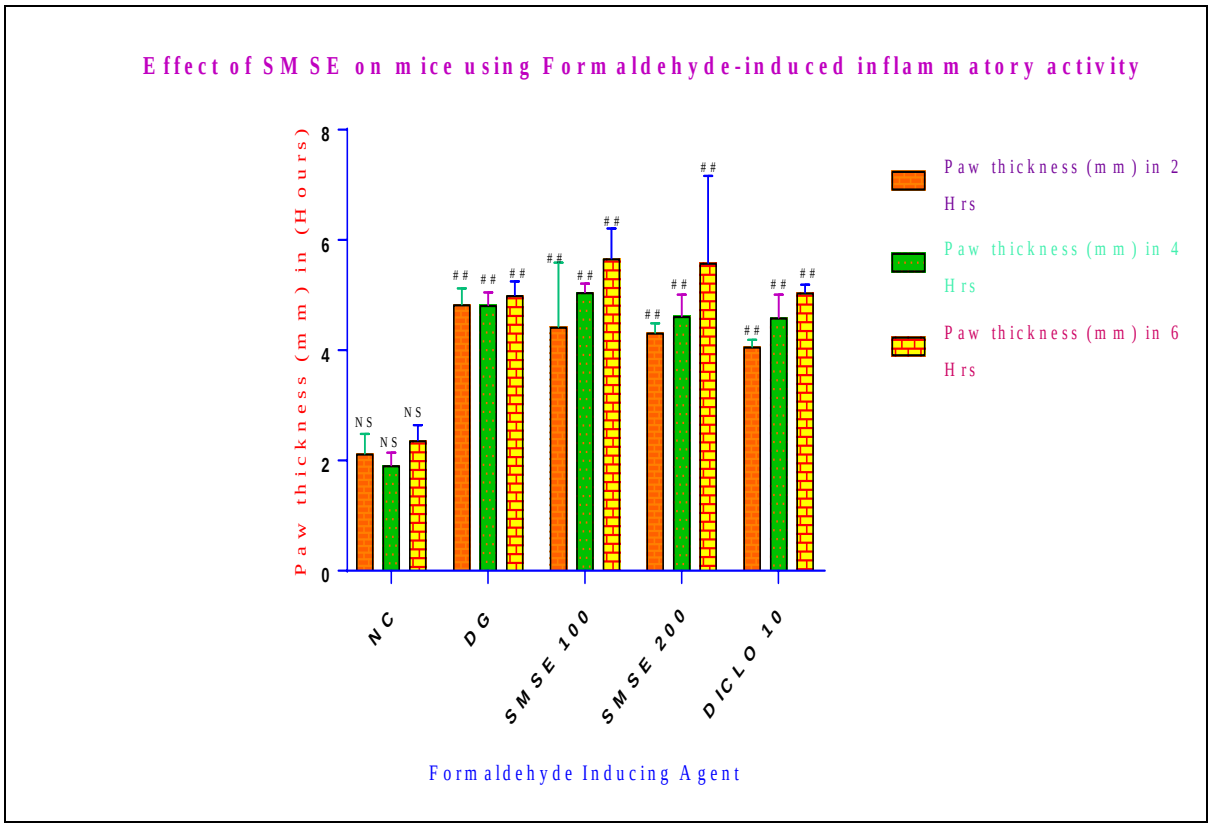
Table 16: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.13 ± 0.35^{NS}	1.92 ± 0.22^{NS}	2.37 ± 0.27^{NS}
DG	$4.84\pm0.28^{\#\#}$	$4.82\pm0.23^{\#\#}$	$5.00\pm0.25^{\#\#}$
SMSE 100	$4.43\pm1.16^{\#\#}$	$5.06\pm0.15^{\#\#}$	$5.67\pm0.54^{\#\#}$
SMSE 200	$4.32\pm0.17^{\#\#}$	$4.62\pm0.39^{\#\#}$	$5.59\pm1.57^{\#\#}$
DICLO 10	$4.07\pm0.12^{\#\#}$	$4.60\pm0.41^{\#\#}$	$5.05\pm0.14^{\#\#}$

Graph 6.2.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents statistical significance against control group.

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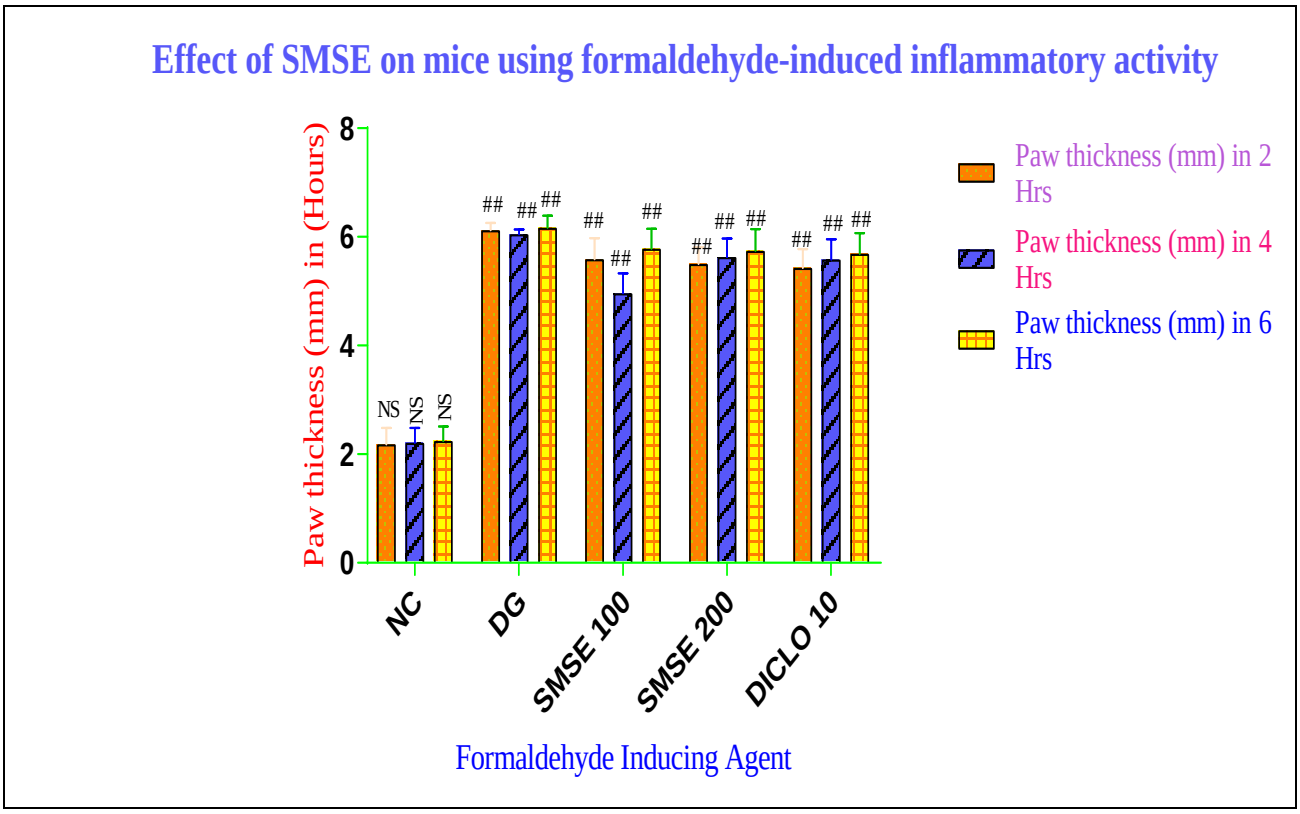
THIRD DAY INDUCING AGENT

Table 17: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.18 ± 0.30^{NS}	2.21 ± 0.27^{NS}	2.24 ± 0.27^{NS}
DG	$6.12\pm0.14^{\#\#}$	$6.05\pm0.09^{\#\#}$	$6.17\pm0.22^{\#\#}$
SMSE 100	$5.59\pm0.39^{\#\#}$	$4.96\pm0.37^{\#\#}$	$5.78\pm0.37^{\#\#}$
SMSE 200	$5.50\pm0.31^{\#\#}$	$5.63\pm0.34^{\#\#}$	$5.74\pm0.40^{\#\#}$
DICLO 10	$5.43\pm0.35^{\#\#}$	$5.58\pm0.38^{\#\#}$	$5.69\pm0.38^{\#\#}$

Graph 6.7.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05

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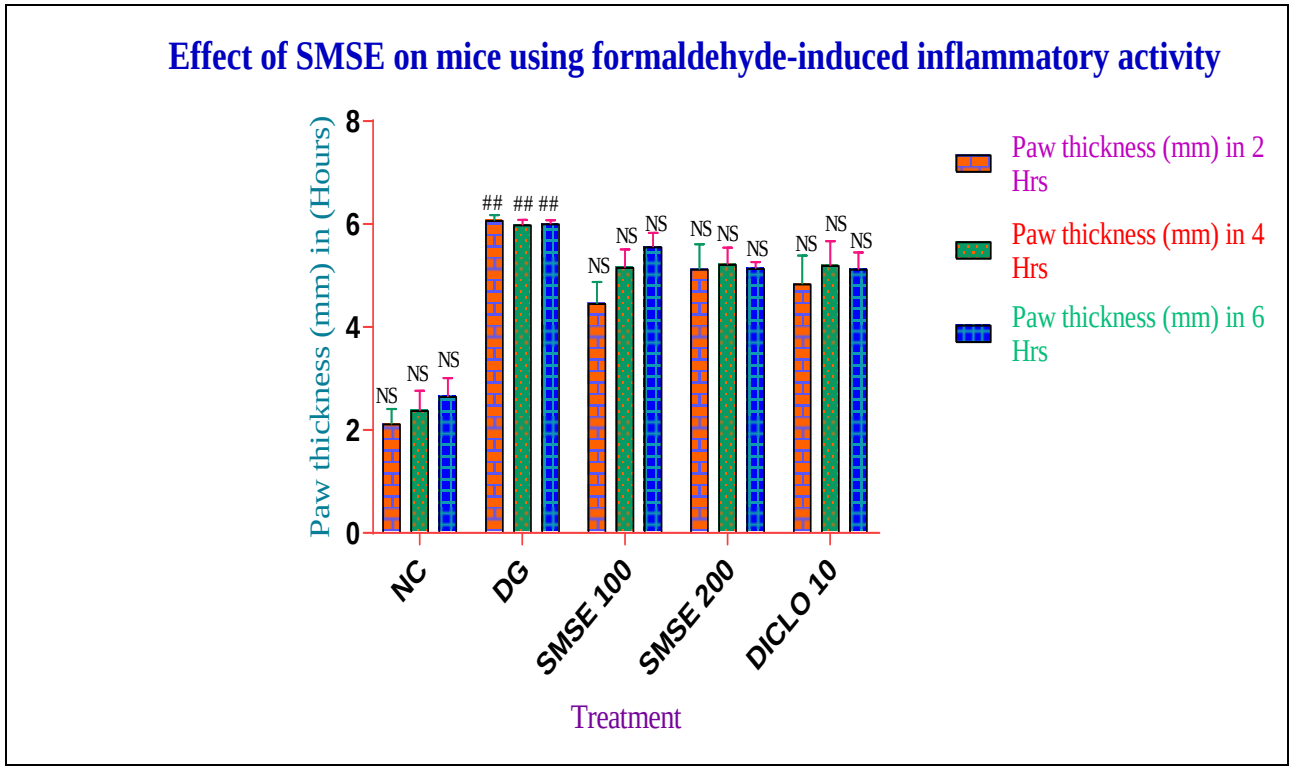
represents statistical significance against control group.

FIRST DAY TREATING AGENT

Table 18: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.13 ± 0.28^{NS}	2.39 ± 0.37^{NS}	2.66 ± 0.35^{NS}
DG	$6.08\pm0.10^{\#\#}$	$6.00\pm0.08^{\#\#}$	$6.02\pm0.06^{\#\#}$
SMSE 100	4.47 ± 0.41^{NS}	5.17 ± 0.34^{NS}	5.57 ± 0.26^{NS}
SMSE 200	5.14 ± 0.47^{NS}	5.23 ± 0.31^{NS}	5.15 ± 0.11^{NS}
DICLO 10	4.85 ± 0.54^{NS}	5.21 ± 0.46^{NS}	5.14 ± 0.31^{NS}

Graph 5.8.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents statistical significance against control group.

SECOND DAY TREATING AGENT

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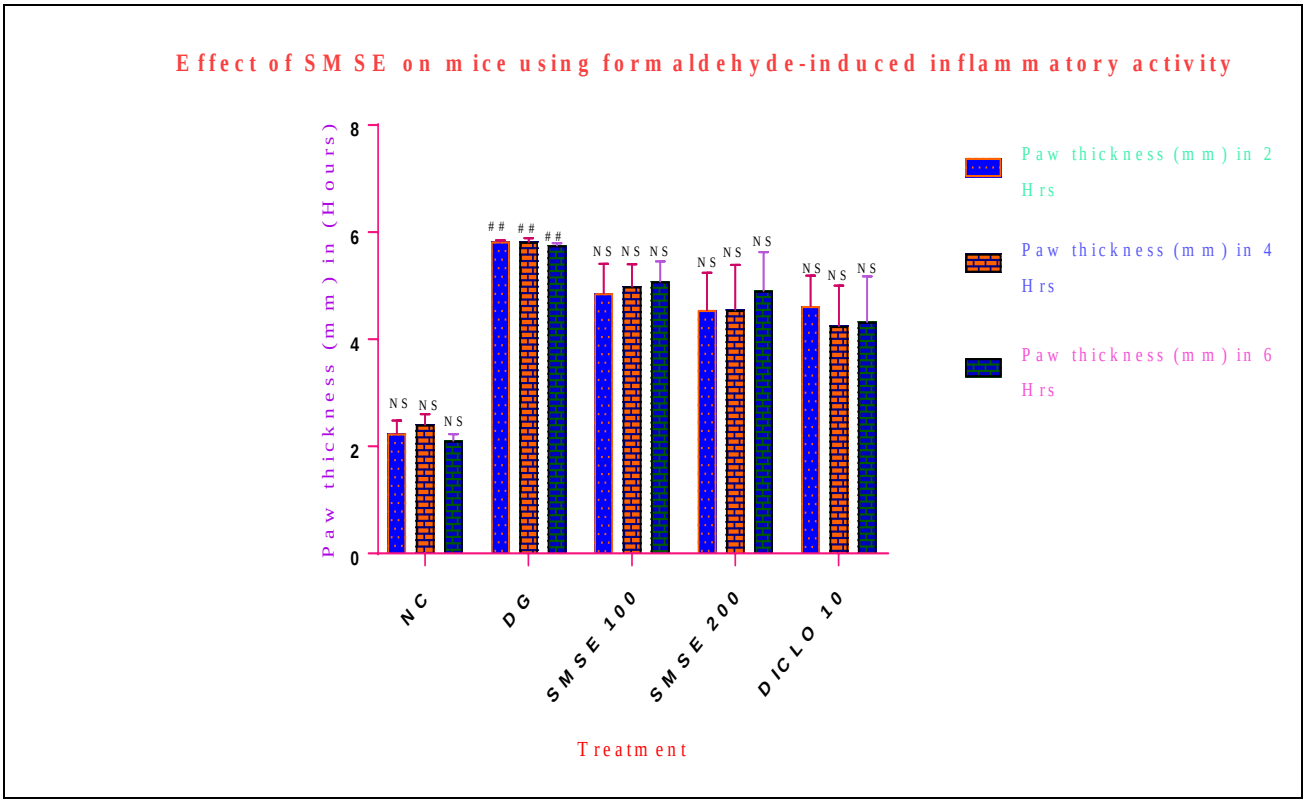
Table 19: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.24 ± 0.24^{NS}	2.41 ± 0.19^{NS}	2.11 ± 0.12^{NS}
DG	$5.83\pm0.02^{\#\#}$	$5.82\pm0.07^{\#\#}$	$5.76\pm0.04^{\#\#}$
SMSE 100	4.86 ± 0.55^{NS}	4.99 ± 0.41^{NS}	5.08 ± 0.38^{NS}
SMSE 200	4.55 ± 0.69^{NS}	4.55 ± 0.84^{NS}	4.91 ± 0.72^{NS}
DICLO 10	4.62 ± 0.57^{NS}	4.25 ± 0.75^{NS}	4.33 ± 0.85^{NS}

Graph 5.9.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05

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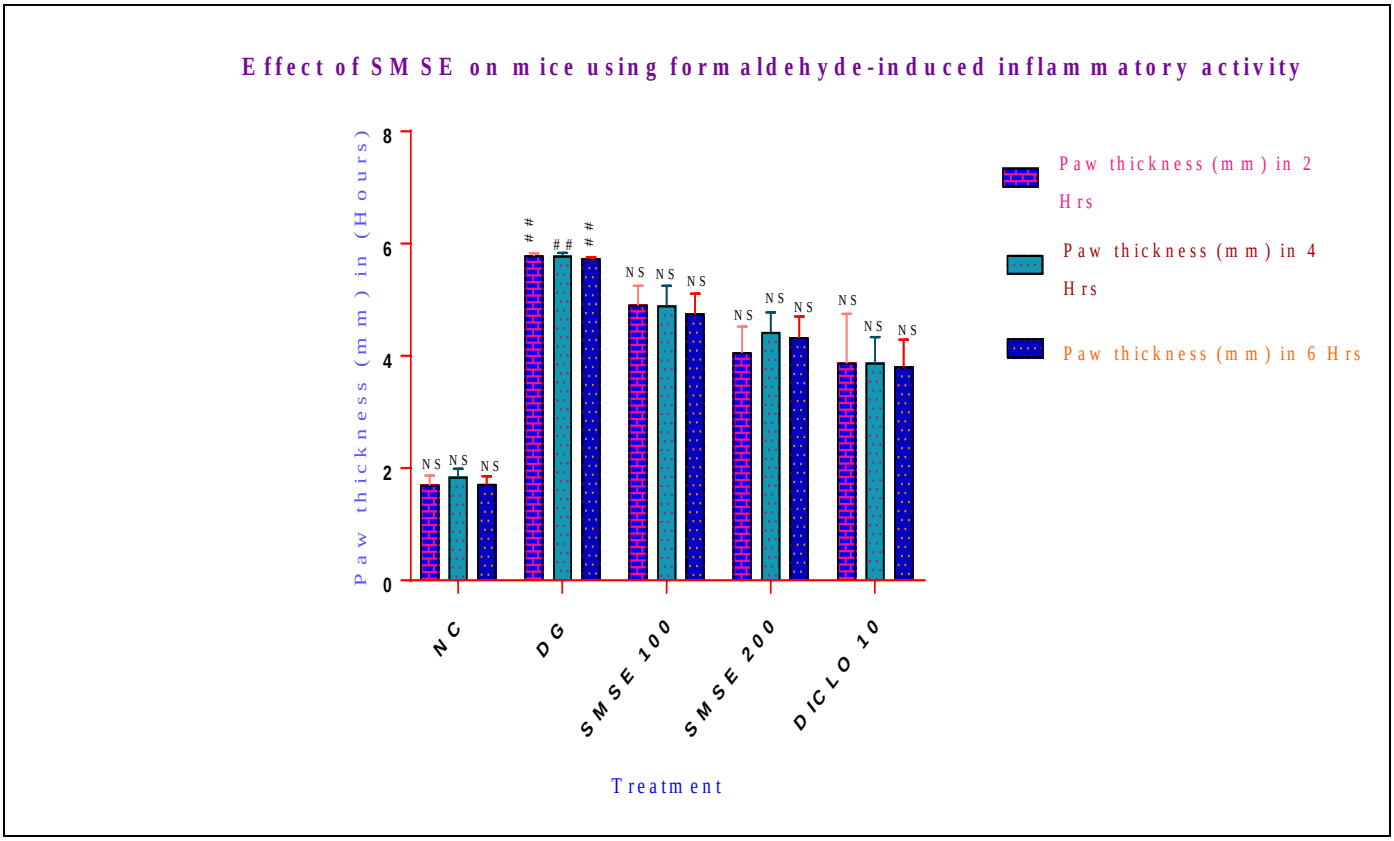
represents statistical significance against control group. **THIRD DAY TREATING AGENT**

Table 20: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	1.71 ± 0.16^{NS}	1.85 ± 0.14^{NS}	1.72 ± 0.14^{NS}
DG	$5.80\pm0.03^{\#\#}$	$5.79\pm0.05^{\#\#}$	$5.74\pm0.02^{\#\#}$
SMSE 100	4.92 ± 0.33^{NS}	4.90 ± 0.35^{NS}	4.76 ± 0.35^{NS}
SMSE 200	4.07 ± 0.45^{NS}	4.43 ± 0.35^{NS}	4.34 ± 0.36^{NS}
DICLO 10	3.88 ± 0.87^{NS}	3.88 ± 0.46^{NS}	3.82 ± 0.47^{NS}

Graph 5.10.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



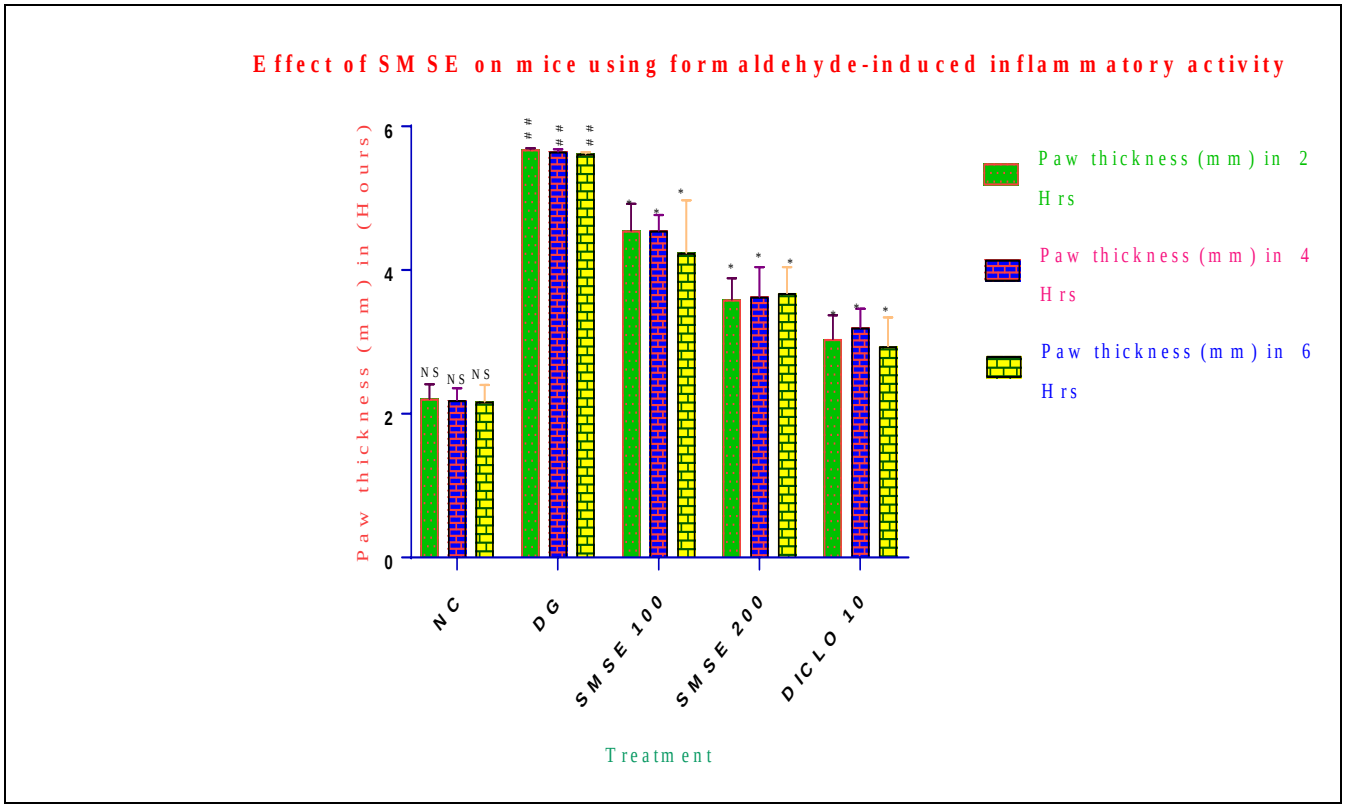
Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents statistical significance against control group.

FOURTH DAY TREATING AGENT

Table 21: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.21 ± 0.20^{NS}	2.19 ± 0.17^{NS}	2.17 ± 0.23^{NS}
DG	$5.68\pm0.02^{\#\#}$	$5.65\pm0.03^{\#\#}$	$5.62\pm0.02^{\#\#}$
SMSE 100	$4.55\pm0.37^{*}$	$4.55\pm0.22^{*}$	$4.24\pm0.73^{*}$
SMSE 200	$3.59\pm0.30^{*}$	$3.63\pm0.41^{*}$	$3.68\pm0.36^{*}$
DICLO 10	$3.04\pm0.33^{*}$	$3.20\pm0.26^{*}$	$2.94\pm0.40^{*}$

Graph 5.11.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



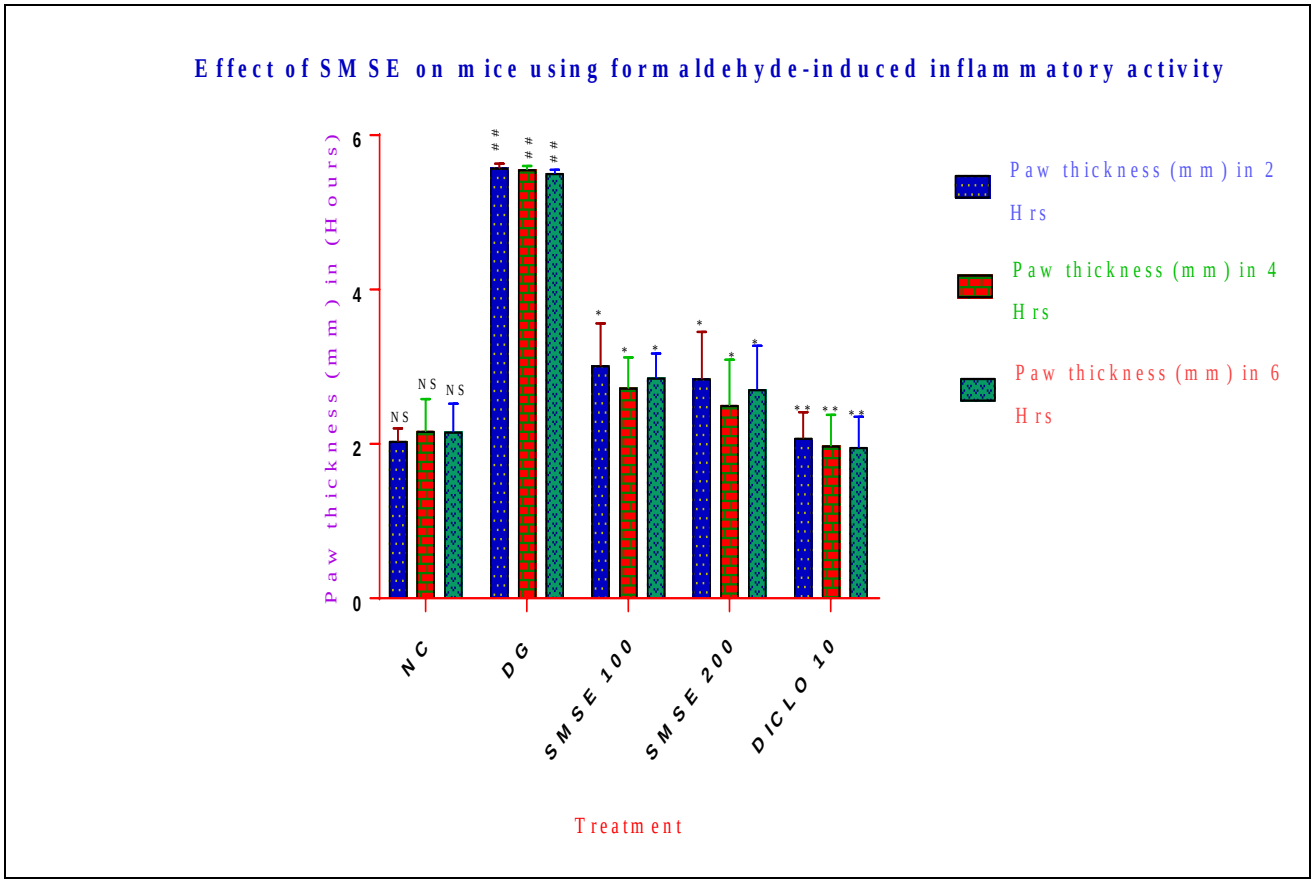
Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05

represents statistical significance against control group. **FIFTH DAY TREATING AGENT**

Table 22: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.04 ± 0.16^{NS}	2.17 ± 0.41^{NS}	2.16 ± 0.36^{NS}
DG	$5.58\pm0.05^{\#\#}$	$5.56\pm0.04^{\#\#}$	$5.51\pm0.04^{\#\#}$
SMSE 100	$3.02\pm0.54^{*}$	$2.73\pm0.39^{*}$	$2.86\pm0.31^{*}$
SMSE 200	$2.85\pm0.60^{*}$	$2.51\pm0.58^{**}$	$2.71\pm0.56^{*}$
DICLO 10	$2.08\pm0.33^{**}$	$1.98\pm0.40^{**}$	$1.96\pm0.39^{**}$

Graph 5.12.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



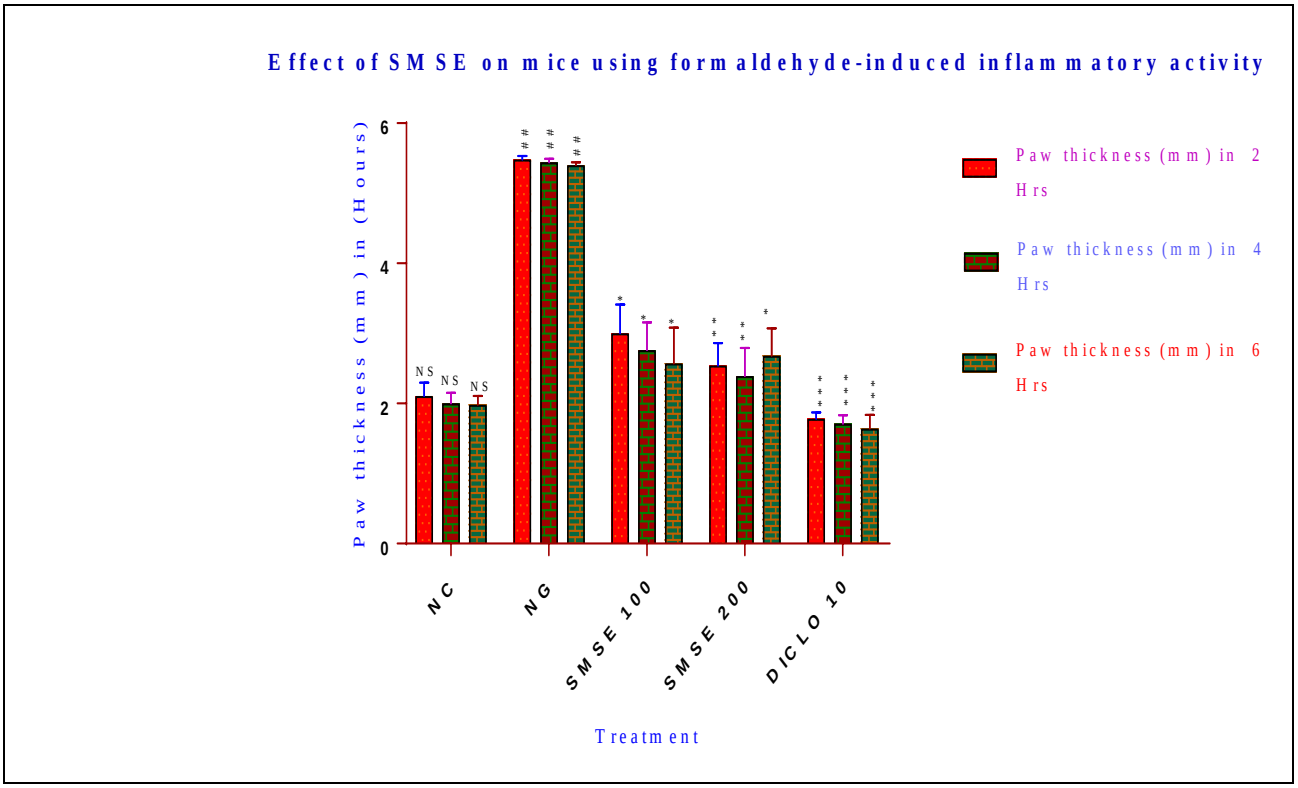
Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents statistical significance against control group, *P<0.0001 represents statistical significance against control group.

SIXTH DAY TREATING AGENT

Table 23: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hours	4 Hours	6 Hours
NC	2.11±0.19^{NS}	2.00±0.15^{NS}	1.98±0.13^{NS}
DG	5.48±0.05$^{\#\#}$	5.44±0.05$^{\#\#}$	5.40±0.04$^{\#\#}$
SMSE 100	3.00±0.41*	2.76±0.40*	2.57±0.51**
SMSE 200	2.54±0.32**	2.39±0.40**	2.68±0.39*
DICLO 10	1.78±0.09***	1.71±0.12***	1.64±0.20***

Graph 5.13.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents statistical significance against control group, *P<0.0001 represents statistical significance against control

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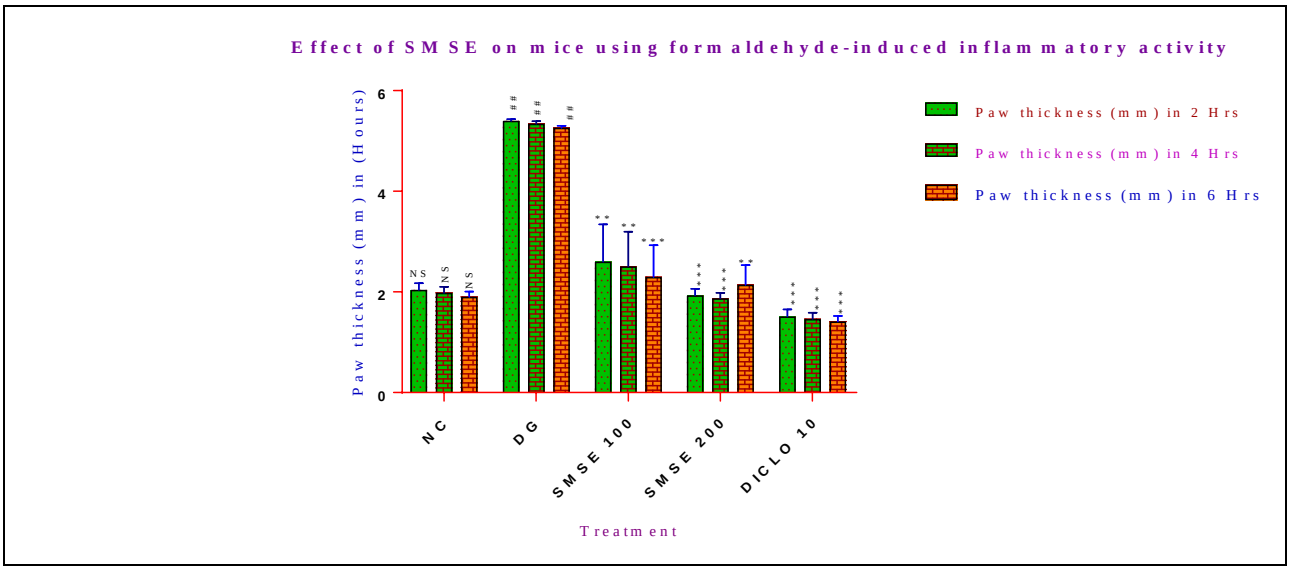
group, **P<0.0003 represents statistical significance against control group, ***P<0.0005 represents statistical significance against control group.

SEVENTH DAY TREATING AGENT

Table 24: Effect of SMSE on mice using formaldehyde-induced inflammatory activity

Groups	Paw edema reading (mm) at different time intervals (Hours)		
	2 Hrs	4 Hrs	6 Hrs
NC	2.04 ± 0.13^{NS}	1.98 ± 0.12^{NS}	1.90 ± 0.11^{NS}
DG	$5.40\pm0.03^{\#\#}$	$5.34\pm0.05^{\#\#}$	$5.26\pm0.04^{\#\#}$
SMSE 100	$2.60\pm0.74^{**}$	$2.51\pm0.69^{**}$	$2.30\pm0.63^{***}$
SMSE 200	$1.93\pm0.13^{***}$	$1.87\pm0.11^{***}$	$2.14\pm0.39^{**}$
DICLO 10	$1.51\pm0.14^{***}$	$1.46\pm0.13^{***}$	$1.41\pm0.11^{***}$

Graph 5.14.1: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity on different values is given as Mean±SEM of experimental animals (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS=Non Significance, ##P<0.05 represents statistical significance against control group, **P<0.0003 represents statistical significance against control group, ***P<0.0005 represents statistical significance against control group.

TNF-α, IL-6 and IL-10 Assay

The cytokines levels of TNF-α, IL-6, and IL-10 in the supernatants are considered as by enzyme-linked immune sorbent assay (ELISA) kits. In short, TNF-α, IL-6, and IL-10 diluted standards or test samples were added into 96-well plates precoated with the affinity purified polyclonal antibodies used in specific for mice TNF-α, IL-6, and IL-10 respectively. The wells were added with enzyme-linked

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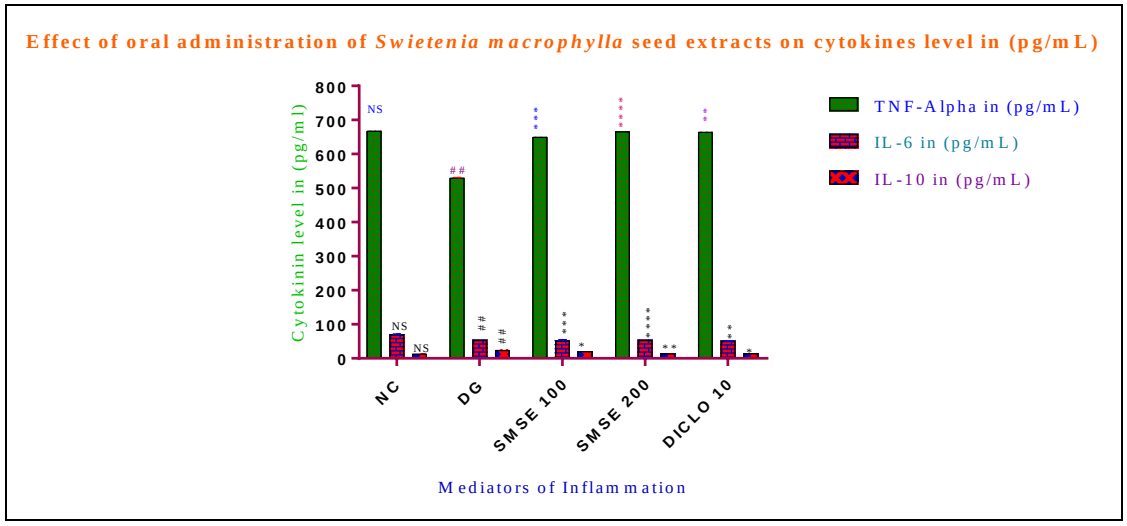
polyclonal antibodies and incubated at 37°C for 60 min, followed by final washes for 5 times. The intensities detected of cytokines level at 450 nm were considered as calculation of substrate solutions and were proportional to the productions of cytokine level; TNF-α, IL-6, and IL-10. Effect of oral administration of Swieteniamacrophylla seed extracts on anti-inflammatory activity cytokines level in (pg/mL) shown in the table number 25.

Table 25: Effect of oral administration of Swieteniamacrophylla seed extracts on anti-inflammatory activity cytokines level in (pg/mL).

S.NO.	Groups	TNF-α	IL-10	IL-6
1	NC	669.23±0.05^{NS}	70.45±0.27 ^{NS}	14.15±0.04 ^{NS}
2	DG	530.75±0.34$^{\#\#}$	54.42±0.19$^{\#\#}$	25.08±0.05$^{\#\#}$
3	SMSE 100	650.77±0.03***	52.57±1.81***	21.66±0.09*
4	SMSE 200	666.77±0.04****	54.4±0.20****	15.22±0.06**
5	DICLO 10	665.76±0.05**	51.51±0.19**	15.73±0.04*

Graph 5.15: Estimation of SMSE as anti-inflammatory activity on mice using formaldehyde-induced inflammatory activity as Swieteniamacrophylla seed extracts on cytokines level in (pg/ml) (n=6).



Where are different values are given as Mean±SEM of experimental animals (n=6), NS= Non significance, ##P<0.05 represents the effect of cytokines level against normal control, *P<0.0001 represents the effect of cytokines level against disease group, **P<0.0003 represents the effect of cytokines level against disease group, ***P<0.0005 represents the effect of cytokines level against disease group.

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Histopathological Examination

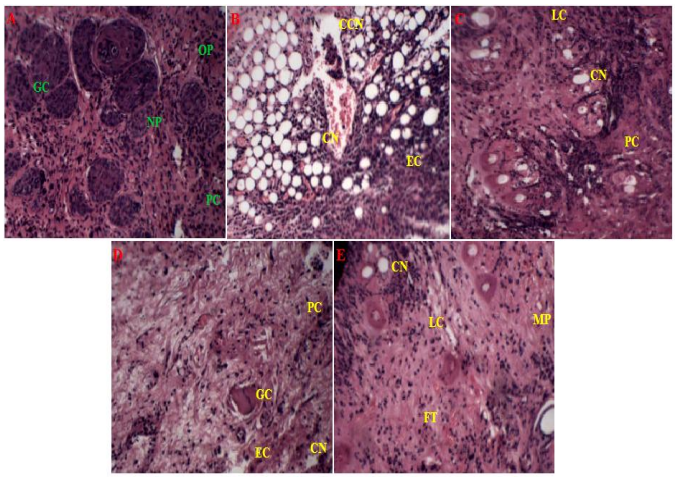

Figure10: Histopathological examinations on formaldehyde-induced inflammatory activity: (a) Normal Control, (b) Disease group, (c) Swieteniamacrophylla seed extract 100 mg/kg, (d) Swieteniamacrophylla seed extract 200 mg/kg, (e) Diclofenac 10 mg/kg.

Abbreviations: PC (Plasma Cells), CCN (Central caseation necrosis), EC (Epithelioid Cells), MP (Macrophases), LC (Lymphocytes), FT (Fibrous cell), GC (Glaints Cell), LP (Neutrophils), CN (Caseation necrosis), EC (Epithelioid cells), OG (Osteoclastic tumour gaint cell), and NP (Neutrophils). The histological changes observed in the inflammation of control mice exhibited normal leg paw tissue, where normal corpuscular and tubular histological structure presented. The Swieteniamacrophylla seed extract exposed mice showed distinctive pathologic alterations such as; degenerated of dilatation in histamine, 5-HT (Serotonin), Cytokines (Interleukins, TNF-α, TNF-β, INF-γ, IIL-17, chemokines, and cytokines) and Neuropeptides.

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Conflicting of Interest

The authors declared no potential conflicts of interest with respect to the authorship, or publication of this review article.

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