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Antipyretic Studies of the Polyherbal Formulations

Nargish Jahan, Diksha Singh
Saraswati Higher Education and Technology college of pharmacy Gahani Varanasi U. P. India

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ABSTRACT:
OAE has qualities that are anti-pyretic. These advantages might result from the presence of phytochemicals such flavonoids, tannins, and terpenes in leaf extracts.The ethanolic leaf extract of OAE has been shown to provide both peripheral and central analgesic effects in a mouse model. When consumed as a leaf extract, OAE has an antipyretic effect on mice and effectively reduces inflammation in a variety of animal models. OAE leaves contain flavonoids and tannins, which may be the reason for the plant's analgesic, antipyretic, and anti-inflammatory properties. If we conducted further research on the OAE plant using other flogestic medicines, we would be better able to comprehend the mechanism underlying the aforementioned activity.

Keywords: Flavonoids, Tannins, Antipyretic, Herbal, Phytochemicals

I. INTRODUCTION:

The most significant types of medicines contain a significant amount of herbs. Since the beginning of human history, herbs have been used as medicine. A few natural medications used in the field of medicine have been mentioned in ancient texts as the Rigved, the Book of Mormon, and the Quran [1]. The Chinese have been using flora and animals as medicine for more than 6,000 years. India has been using herbal therapy for more than a thousand years. The so-called "Father of Medicine," Hippocrates and was the first to rationally explain illnesses [2]. Aromatherapy, as well as naturopathy are examples of Indian medical systems. The majority of medical systems believe a range of internal disorders to be intractable and incurable, yet the use of herbs is a safe and effective method to treat them. Both pain reduction and prevention are its objectives [3].

Many herbal medications for treating human disorders were developed thousands of years ago, either via experience, observation, or trial-and-error approaches. The 'Rig Veda,' written between 2400 and 1800 B.C., has the earliest mention to the usage of plants for medical purposes [4]. In the "Atharva Veda," we observe a more diverse use of medicines. The "Ayurveda," also known as a "Upa Veda," describes the specific features of drugs and their applications in great detail [5]. The "Charka samhita" (600 BC) is another early book on "Ayurveda," which mentions 341 plant products for societal well-being [6]. The "Sushruta Samhita" dealt with medicinal plants as well. Dhanvantari and Nagarjuna were praised for their in-depth knowledge of pharmaceutical medication characteristics. Both ancient Hindu texts and Charaka's historical work mention Rauwolfia, which has acquired worldwide fame. The herb has been touted as an antidote to snake venom and bug stings [8-10].Herbal medications have grown in popularity as a result of their efficacy, convenience of use, low cost, and lack of substantial adverse effects (time tested). Pharmaceutical products are important because phytochemical substances, also known as secondary metabolites, are found in various plant tissues [11]. Among them are polyphenols, alkaloids, essential and edible oils, polymers, mucilage, gums, astringency, and other often utilised components. Plant tissues, such as stems, roots, plants, foliage, and wood, contain such powerful notions [12-15].

II. METHODOLOGY:

Plantcollection and extract preparation:

In the beginning of may 2022, Osmium Sanctum, Azadirachta lndica, Emblica officinalis a plant leaves were harvested.After being collected and authenticated, the leaflets were cleaned to remove any impurities and allowed to fully dry by air drying in the sun. The leaf extract was then thoroughly dry-ground in a mixer.Osmium Sanctum, and Emblica officinalis finely ground was placed evenly in a soxhlet device and recovered with solvents water for 72 hours with periodic shaking at 60°C. The extraction was reduced in volume by evaporation to a very small amount. The ethanol-based extracts of called Osmium sanctum, and Emblica officinalis that produced was subjected to phytochemical investigation [16].

DPPH Assay: In a brief, 0.1mM DPPH was

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produced in 95 percent ethanol. At a concentration of 100g/mL, this solution (1mL) was added to 3 mL of sample (methanolic leaf extract and copper nanoparticles) in ethanol. The mix was thoroughly stirred & placed away at room temperature for 30 minutes. The absorption was then determined at 517 nm with a Spectrophotometry. The test was done three times using sodium bicarbonate as a reference standards reagent. The reactions mixture's decreased absorbance indicated more free radicals scavenge ability [17]. The percent DPPH scavenge efficiency was estimated using equation below:

DPPH scavenging effect (%) = A_0 - A_1 / A_0 × 100

Where A0 is the absorption of the control reactions and A1 is the absorption when the test or standard sample is present [17].

Screening of phytochemicals: The separatehex anethanolic and water extract of Osmium Sanctum, Azadirachtalndica, Emblica officinalis were tested qualitatively for alkaloids, polysaccharides, glycosides, phenolic compounds, peptides, free aminoacids, and triterpenes, among other elements [18-20].

Testforcarbohydrate: Some few drops of α-napthol were added to the filter (20 percent in ethanol). Then 1 milliliter, pure H_2SO_4 was injected all with sidewalls of the slanted test tubes, and the interaction was inspected for the creation of a violet ring.

Glycosides and Anthroquinones analysis: The hydrosylatewas isolated with benzene after a little quantity of ethanolic extract was hydrolyzed with HCL for a few hrs on a boiling water. The benzene layer was exposed to a diluted ammonia solutions & the production of a red pink color was noticed.

Test for flavonoids: Membrane filter strip were immersed in a weak aqueous extract, ammoniated, and the change in color from white -to yellow was noted.

Tests for Phenolic&Tannins compounds: The extractions were divided into 3 parts and diluted in distilled water One portion received 10% sodium chloride, another received 1% gelatine, and the third received gelatine salt reagent. The existence of tannins was indicated by precipitate with the former or both gelatin salt reagent. A high false test is shown by precipitate with salt solution. The introduction of several drop of diluted 1 percent $FeCl_3$ to extracted sample, that is resulted in a bluish or greenish black coloring, verified positive tests.

TestforProteinsandAminoacids: 6-7 droplets of millon reagents (1 g Hg + 9 ml of fuming nitric acid solutions) were added to 2 ml of filtrate, and crimson precipitates were detected.

AcuteToxicityStudies: Wistar rats measuring 150 g to 200 g and S. albino mice weighing 20–25 g were used in this study. The animals originated from the College of Pharmacology Lucknow in India, where they were kept. When the pets arrived, they were allocated at random to the patients being cared for and put in plastic enclosures with rice husks as a bedding. The creatures were housed at 24 °C and between 30 and 70 % relative humidity. We followed the A12:12 light:day cycles. Every animal received unlimited access to water and commercial pelleted food. OECD guideline 423 governs the acceptance of toxicological tests. On the selected albino rats, toxicity tests were conducted. Five groups of the creatures, each containing three creatures, were created. The creatures were fed previously before the acute experimental technique. Rats received oral dosages of extract. For the first four hours following treatment, the animals were closely monitored for behavioral abnormalities such ataxia, hyperactivity, tremor, diarrhoea, fatigue, and sleep. Additionally, they were observed for 15 days after getting the medication to check for any mortality.Rats were given ethanolic extracts of leaf of at concentrations of 1/10 and 1/5 of the maximal acceptable dose (300 as well as 500 mg.kg-1, body weight) to investigate the analgesic, anti-inflammatory effects on the animals Osmium Sanctum, Azadirachtalndica,Emblica officinalis(OAE)were used [21].

Pharmacologicalstudies

Anti-pyreticactivity: The brewer's yeast provoked pyrexia technique was in use to determine the anti-pyretic activity of ethanolic extract. Fever was generated by administering 10.0 $ml.kg^{-1}$ of a 20.00 percent w/v solution of brewer's yeast in NaCl solution under the skin. Only animals had a rectal temperature increase of approximately 1.0^oC after getting a subcutaneous vaccination of 10.0 $ml.kg^{-1}$ of a 20.00 percent w/v brewer's yeast solution in NaCl solution.The research only involved rats with rectal temp raised by minimum 1°C after 18 hours of yeast vaccination. A flexible tail thermometer probe covered with lubricants were used to detect the usual rectal temp of each animal, and the temp was documented utilizing an electronic telethermometer. The experimental group were separated into four subgroups, each of which had six animals. The control group (I) received 0.5 mL saline, the conrol group (II) received 150 $mg.kg^{-1}$

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paracetamol, and group III &IV received doses I & II of ethanolic extracts of test medicines, accordingly [22].

Anti-inflammatory activity: Irish Moss-induced pawedema in rats

The rat (120g - 150g) were put in 4 subgroups (n = 6) for this study. Group I was given 0.50 percent CMC (10ml.kg^{-1}) whereas Group II was given Indomethacin (10mg.kg^{-1}). The ethanolic extracts of Osmium Sanctum, Azadirachta lndica, Emblica officinalis was given vocally to Groups III and IV at doses of 300 mg/kg and 600 mg.kg^{-1}, respectively.The paw width was measured at 1 h, 2 h,3 hand4 hafterIrish Moss vaccination byusingdigitalverniercalipers Acute inflammatory was induced in the mice by administering 0.1 ml of 1percent (w/v) Irish Moss solution into t subplanter area of right hind paw. The animals were given the medication 1 hour before the Irish Moss was given to them (51). Digital vernier callipers were used to assess paw thickness at 1, 2, 3, and 4 hours after Irish Moss administration [23].

Cotton pellets induced granuloma method in rats: Each cottonpellet weighed 5 milligram and was sterilised. The pellets were injected subcutaneous injection via a skin cut on the backs of the animal while they were undergoing ether anaesthesia. The mice in Group-I control group administered CMC (0.5 percent) orally beginning 30 minutes after the cotton pellet was implanted. Group II received Dexamethasone (1 mg.kg^{-1}), while Groups III and IV received 300 mg.kg^{-1} and 600 mg.kg^{-1} of ethanolic extracts of OAE, respectively.This test medications was given once a day for seven days. Diethyl ether was used to sacrifice the rat on the eighth day. The granulomas were taken out and quantified [24].

III. RESULTS & DISCUSSIONS:

Extraction of plant compound:

The extraction of plant secondary metabolites was successfully carried out by using soxhlet apparatus. The extractive yield and ash content as the physicochemical properties were studied where the maximum extraction was obtained in ethanol, then hexane and then water as shown in figure 1.

Further the extracts were studied for the potential antioxidant properties, the best outcome shown in ethanolic extracts as compare to other extracts as shown in figure 2.

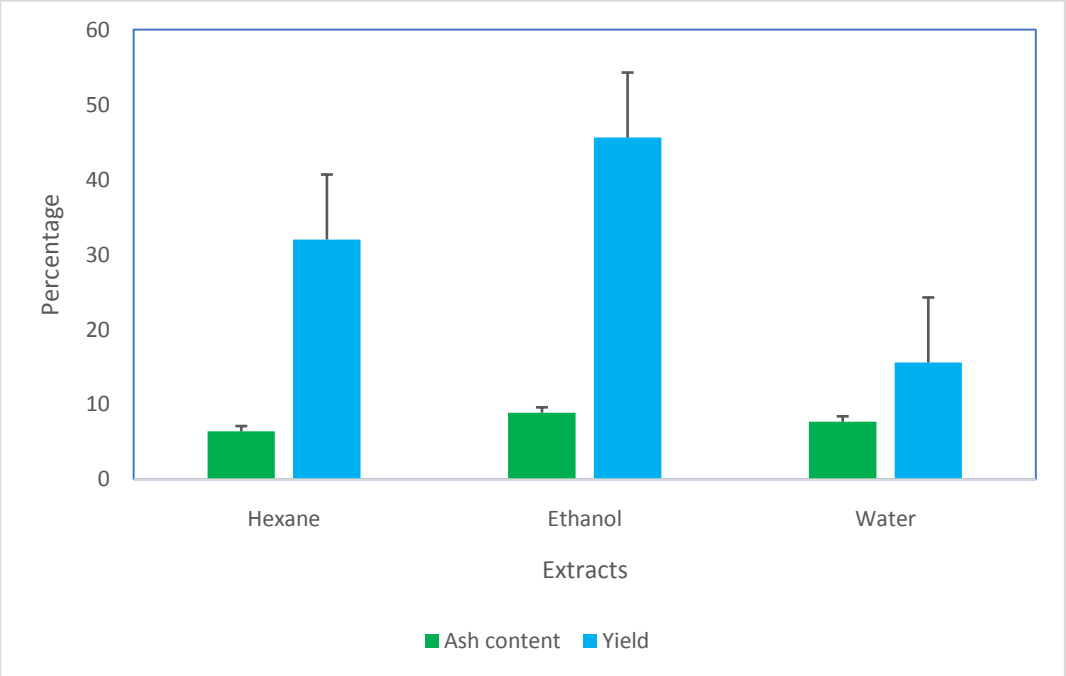

Figure 1: Graphical representation of the Physico-chemical properties.

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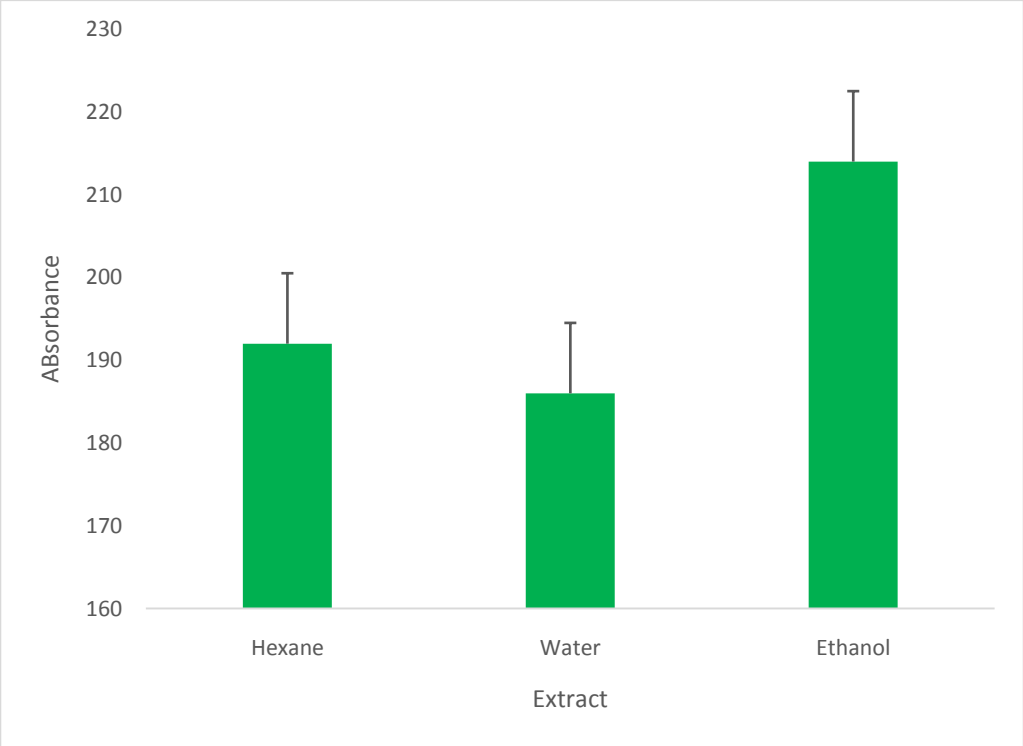

Figure 2: Antioxidant analysis of the extracts

Qualitative phytochemical Evaluation of Osmium Sanctum, Azadirachta lndica, Emblica officinalis.

Table1: Phytochemical screening of Osmium Sanctum Azadirachta lndica, Emblica officinalis

Test	Hexane	Ethanol	Water
Saponins	-	+	-
Glycosides	+	+	+
Steroids	-	+	-
Terpenoids	-	+	-
Flavonoids	+	+	+
Alkaloids	+	+	+
Carbohydrate	-	+	+
Phenols	+	+	+
Tannins	+	+	+
Azadirachta lndica			
Steroids	-	+	-
Glycosides	+	+	-
Terpenoids	-	+	-
Saponins	-	+	-
Alkaloids	-	+	+
Flavonoids	+	+	+
Tannins	+	+	-
Carbohydrate	-	+	+
Phenols	+	+	+
Emblica officinalis			
Steroids	-	+	-
Glycosides	+	+	+
Terpenoids	+	+	+

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Saponins	+	+	-
Alkaloids	+	+	+
Flavonoids	+	+	+
Tannins	-	+	+
Carbohydrate	-	-	-
Phenols	+	+	+

Note: ++:highcontent, +:moderate, -:Negative,

Osmium Sanctum Azadirachta lndica, Emblica officinalis. Hexan, ethanolic and water extract: preliminary phytochemical evaluation Alkaloid, tannin, phenolic compounds, sterol, saponin, proteins and amino acid, and a large amount of flavonoid are found in this plant.

Anti-pyretic activity

Brewer's Yeast Induced Pyrexia in Rats

Table 2 shows the anti-pyretic effectiveness of ethanol leaf extract of OAE towards yeast-induced pyrexia. At concentrations of 200 and 400 mg/kg, the ethanolic leaf extract of OAE. demonstrated a substantial impact towards the Brewer's yeast generated pyrexia technique. The temp of rats treated with the extracts was reduced in a daily dosage manner. When compare to control, the extract generated a considerable reduction.

Table 2:Ethanolic Extract of OAE has Anti-Pyretic Action On Brewer's Yeast Generated Pyrexia In Rats

Treatment	**Rectaltemperature(°C)**				
	18 h after yeast administration	**Temperature after treatment**			
		2hrs	**4hrs**	**6hrs**	**8hrs**
G. I Reference	37.1±0.1	37.4±0.2	37.0±0.1	37.3±0.2	35.2±0.1
G.II Negative References	44.2±0.1	41.4±0.3**	42.1±0.2	37.8±0.1	37.1±0.3
G.-III paracetamol	38.8±0.2	36.9±0.2	37.2±0.2	38.0±0.1	37.4±0.2
G. IV (200mgkg^{-1})	41.2±0.1	37.4±0.3	38.1±0.1	38.0±0.2	39.9±0.3
G. V (400mgkg^{-1})	41.1±0.1	37.8±0.1	37.5±0.2	39.4±0.1	39.5±0.2

****P less than 0.01 vs control, values were mean SEM, (n=6). One-way ANOVA was used to evaluate the data, accompanied by Dennett's test.**

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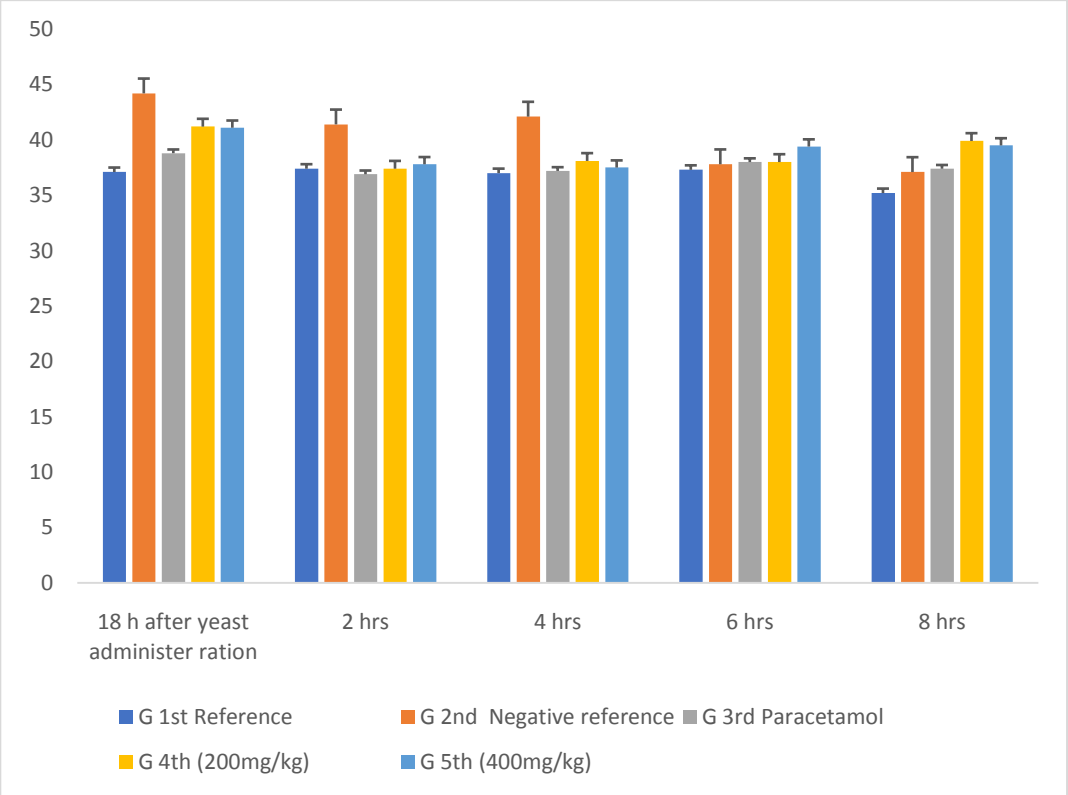

Table 3:On Brewer's Yeast Generated Pyrexia in Rats, Ethanolic Leaf Extraction of OAE has Anti-Pyretic Action.

Anti-Inflammatory Activity

Rats with Irish Moss-triggered Paw Edema

Table 3 shows the anti-inflammatory activity of OAE ethanolic leaf extracts on Irish Moss-triggered hind paw edoema. The ethanolic leaf extracts of OAE demonstrated significant anti-inflammatory action against Irish moss-triggered irritation at dosages of 200 & 400 mgkg-1. The 400 mgkg-1 concentrations had decreased by 48 percent following 3 hours, and the effect had increased (to 52 percent) after three hours of treatment. OAE EtOH extract had significant anti-inflammatory properties that was similar with that of indomethacine (10 mg/kg).

Table 3: Anti-inflammatory activity of EtOH extracts of OAE on Irish Moss triggered paw edema method in Wistar rays.

GROUP	Paw thickness in mm					%Inhibitiona t3hr
	0hr	1hr	2hrs	3hrs	4hrs	
G. I Irish Moss (control)	1.5±0.03	2.5±0.06	4.9±0.06	6.4±0.05	4.8±0.02	-
G.II Indomethacin (10mgkg^{-1})	1.5±0.04	2.3±0.03**	2.9±0.04**	3.1±0.02**	2.2±0.04**	52
G. III(200mgkg^{-1})	1.3±0.02	4.0±0.04	4.2±0.03	4.7±0.01*	3.5±0.04**	27
G. IV(400mgkg^{-1})	1.2±0.01	3.6±0.04**	3.5±0.02*	3.3±0.06**	2.8±0.04**	48

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Note: *P less than 0.05, **P less than 0.01 vs control, values were mean SEM, (n=6). One-way ANOVA was used to evaluate the data, proceeded by Dunnett's test.

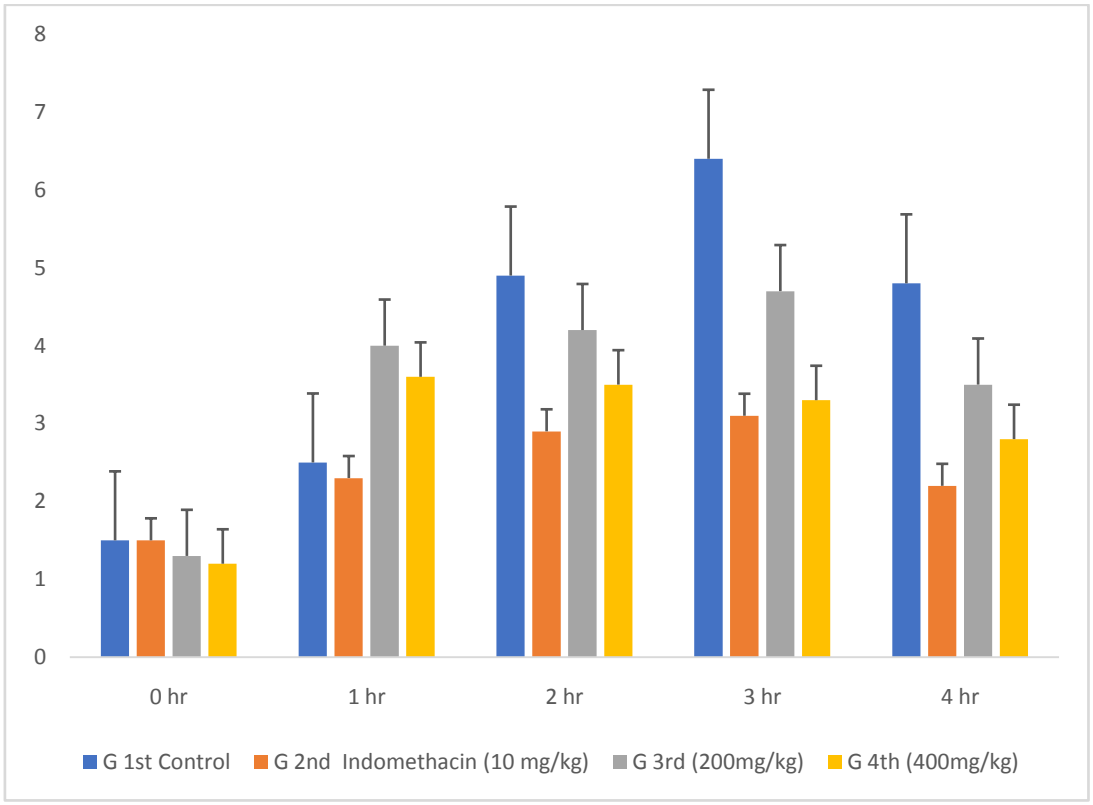

Figure 4:OAE ethanolic leaf extract has anti-inflammatory action in Wistar rats using the Irish Moss generated paw edoema technique.

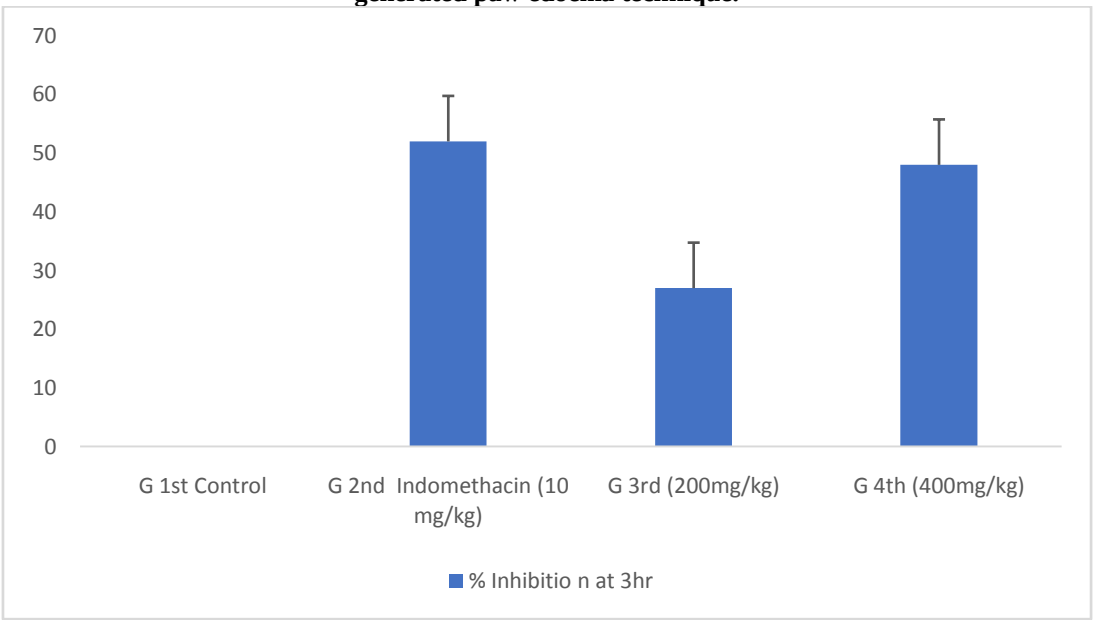

Figure 5: OAE ethanolic leaf extract has anti-inflammatory action in Wistar rats using the Irish Moss triggered paw edoema technique. The results are given as a percentage of inhibition.

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Granuloma Treatment in Rats Triggered by Cotton Pellets

The antiinflammatories activity of OAE EtOH leaf extracts was studied in Wistar rats utilising the cotton pellet generated granuloma method. OAE's EtOH leaf extract at dose of 300 & 500 mgkg^{-1}, It had a significant anti-inflammatory effect. After 7 days, the OAE extraction group's typical weight of the granulomatous tissues surrounding it was significantly lower than that of the opposing group. It was determined that the dose of 400 mgkg-1 was the most efficient one.

Table 4:Anti-inflammation efficacy of an ethanolic extract of OAEcotton pellets in Wistar rats with granuloma pouches

GR.	Granuloma weight(mg)	%Inhibition
I Reference	40.22±0.04	-
II glucocorticoid medication (1mgkg^{-1})	27.91±0.04**	28.8
-III 200mgkg^{-1}	37.15±0.04**	7.4
IV 400mgkg-1	35.47±0.04**	17.1

Note: Values were mean ± SEM, (n=6), **P<0.01 Vs control. Data were analyzed by using One-way ANOVA followed by Dennett's test.

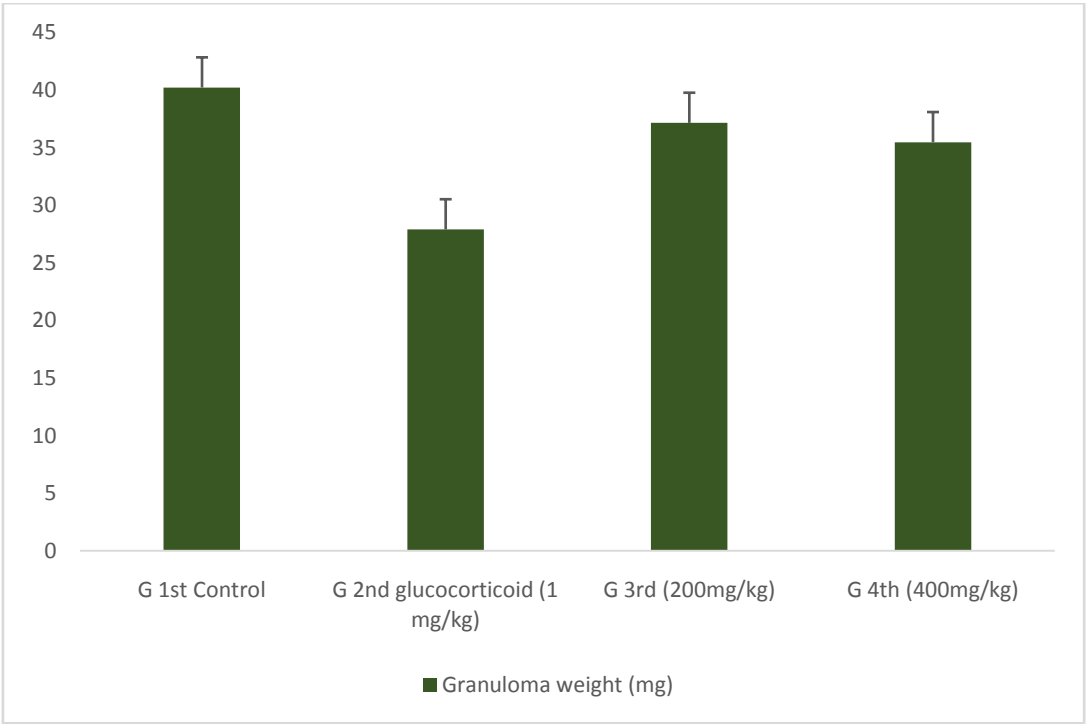

Figure 6:OAE ethanolic leaf extracts have anti-inflammatory effects on cotton pellet-induced granuloma in rats.

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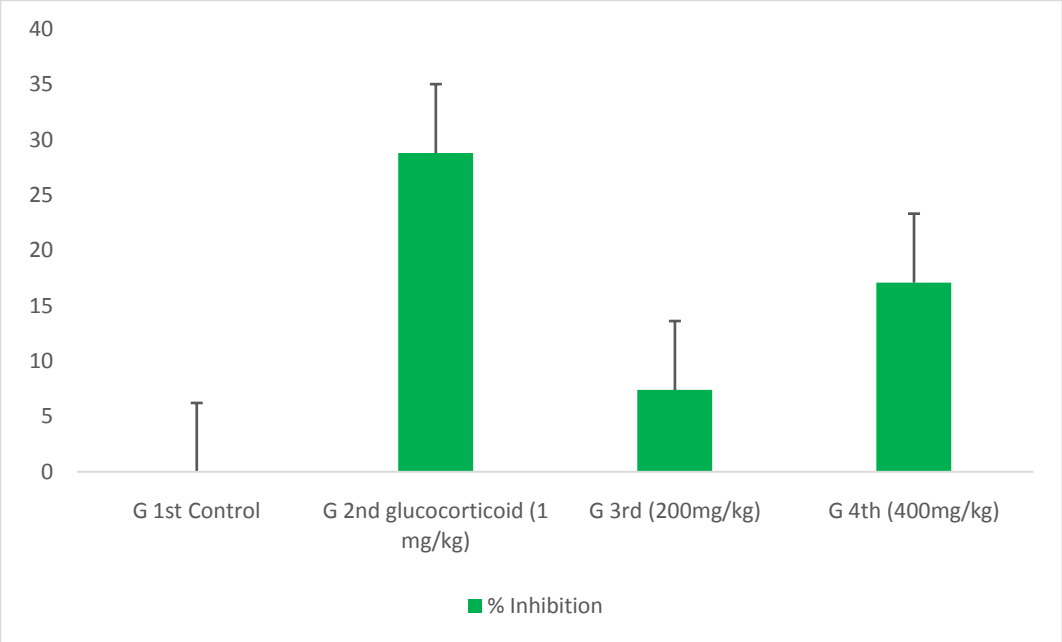

Figure 7:On cotton pellet-induced granuloma in rats, EtOH leaves extract of OAE has anti-inflammatory effect. The percentage inhibition is used to express the results.

Inflammation is a complicated process that typically results in pain & comprises multiple events, including increased muscle permeability, granulocyte & mono nucleate cell movement, and granulomatous tissue development. (63 %) Despite the reality that we all experience pain, it is an unpleasant sensation that can't be precisely measured. Both centralised mechanisms, which are activated by diverse pain perception input, and periphery nociceptive signals afferent neurons that are activated in sick situations may be involved in periphery or neurological pain. Since the hot-plate paradigm has a variety of benefits, such as responsiveness to potent antinociceptives and minimum tissue harm, it was chosen to research peripheral antinociceptive effect. The role of prostaglandins and muscle relaxants in pain has been hypothesised. Phenolic compounds are thought to decrease the synthesis of prostaglandins [25].Many phenolic compounds have been found to have analgesic effects. In additional studies, it has been demonstrated that a number of flavanoids, including rutin, quercetin, have antinociceptive activities. An ethanolic form of OAE contained flavonoid and tannin, which may suppress bradykinin production.

The extract's effectiveness as a primary acting analgesic was confirmed in our analysis by the results of tail immersion tests. The possibility that local interactions with opioid receptors in response to thermal stimuli may be required to demonstrate the antinociceptive activity. The drugs' analgesic activity in a tails immersion experiment suggests that the ethanolic extract has central effects. Overall, the ethanolic form of OAE exerts analgesic effects on both the peripheral and central nervous systems. The ethanolic extract of OAEexhibited anti inflammatory action in a rat paw edoema caused by Irish Moss. Leukocyte movement to wounded tissues is widely established to be an important element of the inflammation response . The initial inflammatory reaction is mediated by histamine & serotonin, but the protracted reaction is mediated by kinins &prostaglandins. Several plants' anti-inflammatory properties have been linked to its significant sterol/triterpene or flavonoid contents. In mice with Irish Moss-triggered paw inflammation, ethanolic extract of OAE. had a considerable anti-inflammatory activity [26].

The inflammatory granuloma is a common reaction to a prolonged inflammation condition and the mass of the pellets has been found to be closely connected to the granulomatous tissue. Prolonged inflammation is caused by the proliferation of proliferative cells.These cells might be granuloma-like or stretch out. In cotton pellet produced granuloma, the OAE extract demonstrated strong anti-inflammatory action and was thus found to be useful in prolonged inflammatory state. It

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demonstrated its ability to reduce the amount of fibroblast and the production of collagen and mucopolysaccharide throughout the formation of granuloma tissue.

Albino rats were given brewer's yeast to provoke fever. Fever was observed 18 hours after yeast insertion since it takes yeast roughly 18 hours to raise body temperature. Pyrexia is induced by injecting Brewer's yeast under the skin, which increases synthesis of prostaglandins. It is thought to be a valuable test for determining the antipyretic activity of organic materials as well as manufactured medications. Bacterial fever is a yeast-triggered pyrexia whose aetiology could be the synthesis of prostaglandins. Reduction of prostaglandin production similar to acetaminophen, could be a method of antipyretic efficacy, and prostaglandin reduction can be accomplished by inhibiting the cyclo-oxygenase enzymatic activity. There are various mediators for pyrexia and of such mediator are accountable for the antipyretic action [27].

The rectal temp of yeast-triggered albino rats was dramatically reduced after oral treatment of OAE. As a result, it's possible that OAE included pharmacologically active components that inhibited prostaglandin release. The ethanol extract of leaves of OAE demonstrated significant antipyretic action towards brewer's yeast generated pyrexia in albino rats after 3 hours of testing. The extract was found to have antipyretic effect that was dose dependent [28, 29].

IV. CONCLUSION:

Utilizing a hot plate, tail immersion, and an acetic acid-triggered writhing mouse model the leaves extract appears to work via central and peripheral pathways of analgesia. The antipyretic effect of the leaves extraction was determined utilizing the yeast triggered pyrexia method, and the anti-inflammatory impact of the leaf extracts was determined using the Irish Moss-triggered paw edoema in mice and cotton pellet granuloma methods.

OAE possesses anti anti-pyretic, properties these benefits could be due to existence of phytochemicals in the leaf extracts such as flavonoid, tannin, and terpenes.

In a mouse model, the ethanolic extract of the leaf of OAE has been demonstrated to produce both peripheral and central analgesic effects. OAE has an antipyretic effect in mice when taken as a leaf extract, and it is effective at reducing inflammation in many different animal models. Flavonoid and tannin found in OAE leaves may be the cause of the plant's analgesic, antipyretic, and anti-inflammatory effects. We would be better able to understand the mechanism underlying the aforementioned activity if we conducted more research on the OAE plant using other flogestic drugs.

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