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ANTI-INFLAMMATORY ACTIVITY OF SIDDHA HERBOMINERAL FORMULATION AJAMOTHASTAKA MAATHIRAI ON CARRAGEENAN INDUCED PAW EDEMA IN WISTAR ALBINO RATS

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ABSTRACT

Objective: The aim of the study was to explore the anti-inflammatory activity of Siddha herbomineral formulation Ajamothastaka maathirai in albino rats, and compared with the standard drug Diclofenac. **Methods**: The Siddha herbomineral formulation Ajamothastaka maathirai indicated for Acid peptic disease was prepared based on GMP (Good Clinical Practice) guidelines. Study procedure was approved by Institutional Animal Ethics Committee (IAEC). The experimental animals were measured for paw edema volume at 1, 2, 3, 4, 5 h using Plethysmometer (Model PLM 01 PLUS UGO Basile, Italy. Edema was expressed as mean increase in paw volume relative to control animals. And then, findings were compared with drug Diclofenac (Standard drug). **Results**: The findings revealed that test drug Ajamothastaka maathirai at higher dosage 200 mg/kg (Group V) had equal effect on anti-inflammatory activity with percentage protection of 93.78% when compared with the standard drug Diclofenac at about 40 mg/kg (Group III) with percentage protection 97.41%. However, the test drug Ajamothastaka maathirai at a higher dosage 200 mg/kg (Group V) with a percentage protection 93.78% was highly effective when compared with lower dosage about 100 mg/kg (Group IV) with a percentage protection 28.36%. Hence, the study resulted that the Siddha herbomineral formulation Ajamothastaka maathirai has an optimistic anti-inflammatory activity with more therapeutic value. **Conclusion:** The study concluded that the Siddha herbomineral formulation Ajamothastaka maathirai has a promising anti-inflammatory activity, probably

due to the presence of biologically active phytocompounds. However, it is important to admit that there are some scientific evidences of the potential actions of these phytocompounds in anti-inflammatory activity.

KEYWORDS: Siddha system, Ajamothastaka maathirai, Acid peptic disease, Anti-inflammatory activity, Diclofenac, Wistar albino rats.

INTRODUCTION

The Siddha system of medicine is the oldest traditional treatment system generated from Dravidian culture and it is flourished in the period of Indus Valley Civilization.[1] It is an ancient system that is practiced in Tamil Nadu in South India and other Tamil-speaking regions of the world. Siddha system of medicine focuses on addressing the root cause of the disease rather than treating the disease symptoms.[2] Herbal plants play an important role in preventing and treating of human diseases.[3] Herbal medicine derived from plant extracts are being increasingly utilized to treat a wide variety of clinical diseases, though little knowledge about their mode of action is available. There is a growing interest in the pharmacological evaluation of various plants used in Indian Traditional System of medicine".[4]

"Acid peptic diseases result from distinctive but overlapping pathogenic mechanisms that typically involve acid effects on diminished mucosal defense. Conditions such as acid reflux, damage the esophageal mucosa, and also potentially cause laryngeal tissue injury with subsequent development of pulmonary symptoms. A peptic ulcer is histologically defined as a mucosal defect that extends to or beyond the muscularis mucosa, with mucosal damage due to pepsin and gastric acid secretion. Most ulcers occur in the stomach and proximal duodenum while less commonly in the lower esophagus, the distal duodenum or the jejunum.[5]

Carragenam was used to induce paw edema volume in Wistar albino rats for the study. During past decade, Carragenam has become much used experimentally mainly for its ability to induce an acute inflammation.[6] Paw edema induced by Carragenam was described by Winter et al.[7] Cardinal signs of inflammation such as edema, hyperalgesia and erythema develop immediately following sub-plantar injection of Carragenam into hind paw, as a result of the action of pro-inflammatory agents such as bradykinin, histamine, prostaglandins, thromboxane, reactive oxygen etc. that can be generated at the site of the insult by infiltrating cells.[8-11]

Over 50 y ago, Diclofenac emerged as an extremely potent nonsteroidal anti-inflammatory drug (NSAID) during massive effort to find effective anti-inflammatory and analgesic medications.[12] It is used as a potent antipyretic, analgesic and anti-inflammatory activity that has been effectively used in the management of mild to moderate pain since the mid-1960s.[13] Hence Diclofenac was used as a standard drug of the current study.

New drug development process must continue through several stages in order to make a medicine that is safe, effective and has approved all regulatory requirements.[14] The process of developing a novel drug is time-consuming and costly. To increase the chances of successfully completing a clinical trial leading to the approval of a new drug, the choice of appropriate preclinical models is of utmost importance. Identifying a safe, potent, and efficacious drug requires thorough preclinical testing, which evaluates aspects of pharmacodynamics, pharmacokinetics and toxicology in in vitro and in vivo settings. Nevertheless, merely a small fraction of investigational new drugs tested in clinical trials after passing pre-clinical evaluation eventually led to a marketed product. Hence, there is a need for optimizing current standard preclinical approaches to better mimic the complexity of human disease mechanisms.[15]

The Siddha system of medicine contains many peculiar herbal, mineral and herbo-mineral combinations for the treatment and management of Acid peptic disease. Among that one such distinct herbomineral formulation was Ajamothastaka maathirai indicated for the treatment and management of Acid peptic disease in Siddha literature "Anuboga Vaithiya Brahmaragasiyam"[4] written by Koshayi swamikal and Munusamy".[16] This Herbomineral combination consists of 7 herbal drugs and 1 mineral drug.

The present study was focused on the pharmacological evaluation of Siddha herbomineral formulation Ajamothastaka maathirai, for its antiinflammatory activity on Carrageenan-induced paw edema in Wistar albino rats. Hence, the objective of the study was to explore and validate the formulation on its capability to reduce the inflammation induced by Carrageenan in Wistar albino rats.

MATERIALS AND METHODS

Study drug

Collection and authentication of drugs

The ingredients present in the formulation were acquired from an indigenous raw drug store.

These raw drugs were verified and authenticated by the Botanist, Department of Medicinal Botany, Government Siddha Medical College, Chennai (Voucher number(GSMC/MB 656-662). Composition of The Siddha Herbomineral formulation Ajamothastaka maathirai. Ajamothastaka maathirai consists of of 7 herbal drugs and 1 mineral drug as per Siddha literature ““Anuboga Vaithiya Brahmaragasiyam”[4] written by Koshayi swamikal and Munusamy are as follows.

INGREDIENTS	BOTANICAL NAME / CHEMICAL NAME	QUANTITY
1.Omam	*Carum copticum*	5 varagan(21 grams)
2.Perungayam	*Ferula asafetida*	5 varagan(21 grams)
3.Kodiveli	*Plumbago indica*	5 varagan(21 grams)
4.Koshtam	*Costus speciosus*	5 varagan(21 grams)
5.Vasambu	*Acorus calamus*	5 varagan(21 grams)
6. Kandubaringi	*Clerodenrum serratum*	5 varagan(21 grams)
7.Indhuppu	*Sodium chloride/Rock salt*	5 varagan(21 grams)
8. Elarisi	*Eletaria cardamomum*	5 varagan(21 grams)

Purification and preparation of sample

Purification of herbal drugs Prior to preparation, all the herbal raw drugs of Ajamothastaka maathirai were purified as per Siddha literature “Sikitcha Rathna Deepam Ennum Vaidhya Nool” and “Sarakkugalin suththi sei muraigal”.

1. Purification of Omam [Carum copticum]: Omam was soaked in a karsunnambu water and filtered, then dried in a sunlight for 3 hours.

2. Purification of Perungayam [Ferula asafoetida]: Perungayam was fried and triturated in a stone mortar to collect a fine powder.

3. Purification of Kodiveli [Plumbago indica]: All the impurities were removed then washed in water and dried it in a sunlight.

4. Purification of Koshtam [Costus speciosus]: All the impurities were removed then washed in water and dried it in a sunlight.

5. Purification of Vasambu [Acorus calamus]: Turmeric paste was applied over the vasambu and heated in a small flame. Then dried and ground in a stone mortar to collect a fine powder.

6. Purification of Kanduparangi [Clerodendrum serratum]: All the impurities were removed then washed in water and dried it in a sunlight.

7. Purification of Indhuppu [Sodium chloride]: Indhuppu was soaked in a vinegar and filtered then dried it in a sunlight for 3 hours.

8. Purification of Elarisi [Elettaria cardamomum]: Skin was removed and the arisi was collected and it was fried and triturated in a stone mortar to collect a fine powder.

Sample preparation

The herbomineral Siddha formulation. Ajamothastaka maathirai consists of 7 herbal drugs and 1 mineral drug was prepared as per Siddha literature ““‘Anuboga Vaithiya Brahmaragasiyam”[4] written by Koshayi swamikal and Munusamy.

• After purification, The purified raw drugs listed in were meticulously ground into a fine powder using a mortar and pestle and seived in a fine cloth separately. Then the fine powders were collected. Finally the fine powders were grinded with sufficient amount of water in a stone mortar.

At last, the karkam was collected and rolled into pills in the size of kazharchikkaai and allowed to dry. [Kazharchikkaai - 2.6gms]. This tablet, named Ajamothastaka maathirai (AM)[4], was then stored in an airtight container for safekeeping.[18]

Ethical approval

Before the initiation of preclinical evaluation, ethical approval for the study procedure was obtained from Institutional Animal Ethics Committee (IAEC) at Department of Pharmacy, C. L. Baid Metha college of Pharmacy, Thorapakkam, Chennai-6000092. All the study procedure were performed as per the guidelines and ethical principles of ethics committee for experimentation using animals under proper care and control. (IAEC NO. 11/321/PO/Re/S/01/CPCSEA/dated 12/07/2023).

Experimental animals

Selection of experimental animals

For study the healthy, young adult Wistar albino female rats were taken. They were nulliparous, non-pregnant about 6-8 w old with weight of about 150-200 gm, the weight of the animals fell in the mean interval of+20% of mean weight. Female rats were chosen because of their sensitivity to the treatment.[17] Experimental animals were obtained from Mass biotech, Chennai.

Housing and feeding conditions of experimental animals

Animals involved in the experiment were housed in polypropylene cages, with husk bedding. The temperature maintained was about 22 °C+3 °C and relative humidity about 50-60%. In 24 h, 12 h of light cycle and 12 h of dark cycle were maintained. Conventional laboratory feeds were fed with an unlimited supply of drinking water. Prior to the administration of

drugs, acclimatization was done followed by a veterinary examination of all the experimental animals. And then, all the experimental animals were kept as group caged with proper study procedure.

Preparation of experimental animals

For an experiment, the animals were randomly selected and kept in individual cages marked with picric acid for identification 7 d before to inducing inflammation. The animals were divided into 5 groups (each group contains 6 animals). They were grouped as follows.

ϖ Group I (Control)-received 3% of gum acacia 10 ml/kg per oral administration.

ϖ Group II (Carrageenan)-received 0.1 ml of 1% w/v suspension of Carrageenan (Subcutaneous injection)

ϖ Group III (Standard)-received Diclofenac 40 mg/kg per oral administration.

ϖ Group IV (Low dose)-received Ajamothastaka maathirai 100 mg/kg per oral administration.

ϖ Group V (High dose)-received Ajamothastaka maathirai 200 mg/kg per oral administration.

Induction of paw edema volume

The study was performed at C. L. Baid Metha College of Pharmacy, Chennai. After the preparation of animals, all the drugs were administered orally and the volume of the medicaments were kept constant at 10 ml/kg body weight of the experimental animals. Thus, Group I received 3% of gum acacia orally, Group II received 0.1 ml of 1% w/v suspension of Carrageenan injected subcutaneously, Group III received the standard drug In Diclofenac 40 mg/kg orally, Group IV received low dose (100 mg/kg) of Ajamothastaka maathirai test drug orally and Group V received high dose (200 mg/kg) of Ajamothastaka maathirai orally. After 1 h of dosing, 0.1 ml of 1% w/v suspension of carrageenan was injected into the sub-plantar region of the left hind paw to all the groups involved in the study. Then the paw edema volume was measured in 1, 2, 3, 4 and 5 h using a Plethysmometer (Model PLM 01 PLUS UGO Basile, Italy. Edema was expressed as the mean increase in paw volume relative to control animals. Anti-inflammatory activity was measured as the percentage reduction in edema level when drug was relative to control.[18]

Analysis of reduction in paw edema volume

After injection of carrageenan to the subcutaneous region of left hind paw, the paw edema

volume was analyzed for the experimental animals. The paw volume was measured up to the tibiotarsal articulation measured at 0, 1, 2, 3, 4, 5 h and denoted as mean+SEM. The percentage protection of test drug Ajamothastaka maathirai was calculated by formulae (T2-T1/T2) X 100, Where T1 denotes normal control and T2 denotes drug used for test.

RESULTS

The paw edema volume of experimental animals at different time intervals were indicated in table 1 and the percentage protection of test drug Ajamothastaka maathirai were described in table 2 and fig. 3.

Table 1: Paw edema volume at different time intervals.

Group	Dose	Initial paw volume	Change in paw edema mm at different time intervals				
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr
I	Control	1.20 ± 0.14	1.20±0.14	1.20±0.14	1.20±0.14	1.20±.14	1.20±0.14
II	Carrageenan	1.21± 0.17	1.96 ± 0.81	2.30 ± 0.12	2.41 ± 0.16	2.56 ± 0.19	2.68 ± 0.27
III	Diclofenac	1.11± 0.06	2.36± 0.25	1.52± 0.16	1.48± 0.19	1.46± 0.32	1.25 ± 0.16
IV	Low dose	1.49 ± 0.13	1.69 ± 0.42	1.74 ± 0.62	1.78 ± 0.32	1.66 ± 0.82	1.59 ± 0.52
V	High dose	1.74±0.32	2.88± 0.33	2.94± 0.42	2.84 ± 0.54	2.66 ± 0.78	1.82± 0.22

The paw volume up to the Tibiotarsal joint articulation was measured at 0, 1, 2, 3, 4, 5 hrs

Paw edema volume measurements denoted as Mean+SEM; n=6 rats.

Table 2: Percentage protection of Ajamothastaka maathirai.

Group	Initial paw volume	5 hr in mm	Difference in paw volume	Percentage protection
I	1.20 ± 0.14	1.20±0.14	0.00	100
II	1.21± 0.17	2.68 ± 0.27	1.47	14.53
III	1.11± 0.06	1.25 ± 0.16	0.14	97.41
IV	1.49 ± 0.13	1.59 ± 0.52	0.1	28.36
V	1.74 ±0.32	1.82 ± 0.22	0.08	93.78

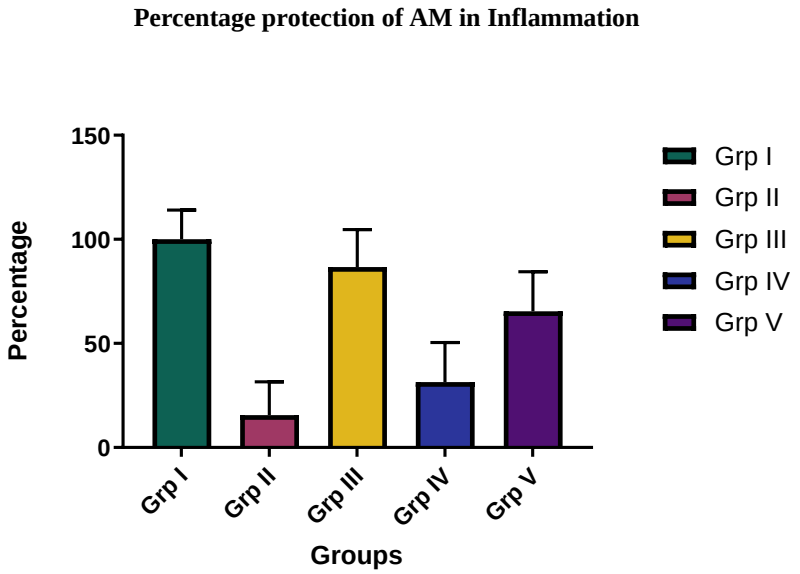

Fig. 3: Percentage protection of Ajamothastaka maathirai, [N= 6 rats, Percentage protection in control = 100%, Carrageenan =14.53%, Standard (Diclofenac) = 97.41%, Low dose (Ajamothastaka maathirai) = 28.36%, High dose (Ajamothastaka maathirai) = 93.78%]

DISCUSSION

Carrageenan-induced rat paw edema is used widely as a working model of inflammation in the search for new anti-inflammatory drug.[19] From the results obtained, the test drug at the lower dose of 100 mg/kg have mild inhibition on inflammation induced by carrageenan when compared to standard drug with percentage protection of 28.36%at 5th h. However, at higher dose, the test drug Ajamothastaka maathirai had equal effect on reducing inflammation with percentage protection of 93.78%, when compared with standard drug Diclofenac contains the percentage protection of 97.41% at 5th h. This ensured an anti-inflammatory activity of Siddha herbomineral formulation Ajamothastaka maathirai in Carrageenan induced paw edema volume in Wistar albino rat.

The development of edema in the paw of the rat after the injection of carrageenan is due to release of histamine, serotonin and prostaglandin.[21] Thus, the anti-inflammatory effect of Ajamothastaka Maathirai may be due to the presence of many phytocompounds in its ingredients. Many prior studies were published regarding the anti-inflammatory activity of individual drugs in Ajamothastaka Maathirai. In C.copticum, the plant and its constituents,

thymol and carvacrol. the plant and its constituents have therapeutic values in several inflammatory and immunological disorders as well as in the oxidative stress conditions.[21] In F.asafoetida, effects may be due to its effective constituents such as monoterpenes, flavonoids and phenolic components that have antioxidant properties and inhibit lipoxygenase activity.[22] The unique ability of C.specious, they decreased proinflammatory cytokines (IL-1β, IL-6, and TNF-α) with decreased level of the target enzymes (COX-2 and lipoxgenase-5) and subsequent reduction of its inflammatory product (PGE2).[24] The 80% ethanolic extract of Acorus calamus possesses anti-inflammatory activity which is probably related to the significant reduction of various biochemicals, viz. histamine, 5-HT, various kinins which are involved in early phases of inflammation.[25]

The root of C.serrratum showed significantly higher free radical scavenging and anti-inflammatory effects in studied assays. The observed activities might be attributed to the higher content of polyphenols present in EFCSR fraction of roots.[26] P. zeylanica extract showed significant action against carrageenan-induced rat paw edema in a dose-dependent manner.[23] E. cardamom extracts have a therapeutic potential against periodontal infections through their anti-bacterial and anti-inflammatory properties.[27] The phytocompounds present in herbomineral drugs of Ajamothastaka Maathirai individually contains anti-inflammatory property by its inhibitory effects in histamine, prostaglandin and seratonins. These scientific evidences acquired from research articles further ensured the antiinflammatory activity of the Siddha herbomineral formulation Ajamothastaka Maathirai.

CONCLUSION

From the results and discussion, the Siddha herbomineral formulation Ajamothastaka Maathirai has potent anti-inflammatory activity without any adverse effects. This activity mainly due to the presence of phytocompounds of herbal drugs present in Ajamothastaka Maathirai which has an inhibitory action over pro-inflammatory agents such as prostaglandins, serotonin and thrombaxes. By this the current study concluded and ensured the anti-inflammatory activity of the Siddha herbomineral formulation Ajamothastaka Maathirai. Hence, it will be a promising drug of choice for the management and treatment of Acid peptic disease and various other inflammatory disease.

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Chennai, Tamil Nadu.

CONFLICT OF INTERESTS

Authors have declared no competing interests exist.

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