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Research Article

EVALUATION OF ANTIPYRETIC ACTIVITY OF SIDDHA HERBOMINERAL FORMULATION - *SURANGUSA PARPAM*

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ABSTRACT

The aim of the present study was to assess the antipyretic activity of Siddha herbo-mineral formulation *Surangusa Parpam* at the dose level of 15mg/kg and 35mg/kg body weight, orally, in brewer yeast induced fever model Wistar rats. Fever was induced by subcutaneous injection of 10ml/kg of 20% w/v aqueous suspension of brewer's yeast into the nape of the rat's neck. After eighteen hours feverish animals were treated with *Surangusa Parpam* 15mg/kg and 35mg/kg body weight, orally, and rectal temperatures were evaluated at 0, 1, 2 and 3 hours post-treatment by inserting a well-lubricated bulb of the clinical thermometer. *Surangusa Parpam* showed a significant decrease in the elevated body temperature of rats that remained sustained throughout the tested time points from 1 to 3 hours in the used model. 35mg/kg body weight dose level showed significant inhibition of elevated body temperature when compared with the standard control. These results indicate that the Antipyretic activity of *Surangusa Parpam* and in addition to its well-established anti-inflammatory activity possesses significant antihistamine activity that may be beneficial in symptomatic relief when it is used in the therapy of allergic and inflammatory disorders.

INTRODUCTION

The hypothalamus regulates body temperature with a delicate balance between heat production and heat loss through set-point control. Infection, tissue damage, inflammation, graft rejection, malignancy and other diseases may elevate the set point to induce fever.[1] Fever is a well-known finding in almost all infectious disease conditions and inflammatory disorders. Although uncomfortable, or even risky if 4 degrees over normal because of dehydration, strained heart and impaired respiration; however, it gives an alarm warning of infection or a risk to the body. Mastering fever besides treating the specific infectious agent that causes the disease is considered a critical and important issue in therapy for the safety and welfare of the animal and human patient subjects. Classically, the genesis of fever or pyrexia; upon exposure to infectious agents such as bacteria, viruses, fungi and some parasites or to mechanical injuries; is induced by inflammatory mediators (that is, prostaglandins and pro-inflammatory cytokines) that are released by affected tissue and activated immune cells.[2] Elevation of the body temperature occurs when the concentration of prostaglandin E2 (PGE2) increases within parts of the brain. The mechanism of antipyretic drugs is inhibiting the cyclooxygenase (COX) activity and consequently reducing the levels of PGE2. Synthetic antipyretic drugs have side effects.[3] Therefore, it is worth to searching herbal medicines that are equally efficacious and comparatively side effects free, as substitutes for synthetic drugs, in recent years herbal medicine is a major component in all traditional medicine systems, and a common element in Siddha, Ayurvedic, Homeopathic, Naturopathic, Traditional Chinese medicine, and Native American

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medicine. Considerable efforts have been directed towards the development of natural products from various plant sources.[4]

In the Siddha system of medicine, many formulations are mentioned for respiratory illness. *Surangusa Parpam (SP)* is one of the Siddha drugs mentioned in the Siddha text, *Anuboga vaithiya Navaneetham* part III pg.no.90, and it is useful to treat kapha diseases like *kasam* (cough, asthma), *Suram* (fever), and *Ulaimanthai* (intestinal TB) etc. The ingredients of *Surangusa Parpam (SP)* are *Manosilai* (arsenic di sulphide), *Sangu* (conch – Shell – *Turbinella pyrum L*), and *Milagu* (Pepper - *Piper longum*). When traditional literature was reviewed, it revealed that *Manosilai* (arsenic disulphide), has antimicrobial,[5] and anti-asthmatic properties[6] *Sangu* (conch – Shell – *Turbinella pyrum L*) has anti-inflammatory and anti-pyretic properties,[7] and the research articles revealed that the individual of some ingredients of *SP* possess antipyretic activity but as a finished product no pharmacological activities had been carried out for this formulation. Hence we selected the drug *SP* to evaluate the Antipyretic activity.

MATERIALS AND METHODS

Ingredients of *SP*

1. Purified *Manosilai* (Arsenic disulphide) - 4 *Varagan* (14g)
2. Purified *Sangu* (Conch – Shell – *Turbinella pyrum L*)- 4 *Varagan* (14g)
3. Purified *Milagu* (Pepper - *Piper longum*) - 4 *Varagan* (14g)

Uses

1. *Suram* (Fever)
2. *Kaasam* (Cough)
3. *Ulaimaanthai* (Tuberculosis of the lung or incurable internal abscess)

The raw drugs were procured from a well-reputed country shop in Parry's Corner, Chennai. All the ingredients were purified and the medicine was prepared in the Gunapadam (Siddha Pharmacology) laboratory of the National Institute of Siddha, Chennai–47. The plant material *Milagu* (Pepper - *Piper longum*) was identified and authenticated by the Assistant Professor, Department of Medicinal Botany, National Institute of Siddha. The raw drug *Manosilai* (Arsenic disulphide) and *Sangu* (Conch – Shell – *Turbinella pyrum L*) was authenticated by the Faculty member, Department of Gunapadam, National Institute of Siddha, Chennai – 47.

Purification of the Raw Drugs

All the drugs mentioned here were purified as per the Siddha literature.

1. **Purification of *Manosilai* (Arsenic disulphide)**
   Red orpiment (35 grams) is made into small pieces and kept soaked in 175 g of fermented buttermilk in a clay vessel. It was isolated and kindling was done frequently. In the evening it is washed in water. The same procedure was repeated three times to get purified form.[8] [Fig 1.]
2. **Purification of *Sangu* (Conch – Shell – *Turbinella pyrum L*)**
   Take equal quantities of limestone and fuller earth and add water eight times the weight of the conch. Put the conch into it and boil it well to get it purified.[8] [Fig.2]
3. **Purification of *Milagu* (Pepper - *Piper longum*)**
   Piper nigrum is soaked in buttermilk for 1 ½ hours and then it is dried and roasted to get it purified.[9] [Fig. 3]

Method of Preparation

The above ingredients are soaked in goat urine 2 ½ *Palam* (87.5g) and kept for 3 days. On the fourth day, the contents are rubbed for 3 days with the same urine in which they are soaked. Then they are made into pellets and dried. The dried pellets are placed in a mud plate which is then covered by a similar mud plate. The margins are covered by a mud-pasted cloth, dried and then subjected to *Pudam* (incineration) with cow dung cakes which are 20 times the weight of sealed mud plates. Again the process is repeated once. Being cooled, the lid is opened and the processed medicine thus obtained is collected and kept in an airtight container.[10] The dosage of the SP is 1–2 *Kundri* (130–260mg), Twice a Day, After food with An adjuvant is Honey. [Fig. 4]

Ethical Clearance

Before the commencement of the study, the Antipyretic activity experimental protocol was approved by the Institutional Animal Ethics Committee of the National Institute of Siddha, Chennai– 47, with approval number NIS/IAEC-V/09082017/07.

Animals

The present study was conducted in experimental animals, i.e., Albino Wistar rats. The animals were kept in polypropylene cages with bedding of husk in the animal house. Wistar rats of either sex weighing between 140 and 160 g (6 – 8 weeks old) were chosen for the carrageenan-induced paw oedema model. They were maintained under standard laboratory conditions (12h light and dark cycle), temperature (24°C ± 3°C), humidity (30-60% ± 10%) with access to food and water ad libitum as per the Organization for Economic Cooperation and Development guidelines, revised draft guidelines 425 and by the Committee for the Purpose of Control and Supervision of Experiments on Animals.[11] The acclimatization period is about 2 weeks before subjecting them to experimentation.

Assessment of Antipyretic Activity – Brewer yeast-induced method

The antipyretic activity animal model was a slightly modified method described by Adams et al.[12]

Total 24 Wistar albino (12 Male + 12 Female) rats weighing 140gm to 160gm were used in this study. Rats were divided into 4 groups, consisting of six animals for each group. Before yeast injection, the rectal temperature of rats was recorded by inserting a well-lubricated bulb of the clinical thermometer to a depth of 2 m into the rectum and after recording, 10 ml/kg of 20% w/v aqueous suspension of brewer's yeast was given subcutaneously below the nape of the neck.[13] After 18 hours of yeast injection, rats which showed a rise in temperature of at least 0.5-1°C were taken for the study. The honey was administered orally to the control groups (Group I) of animals and paracetamol at the dose of 150mg/ml was administered orally to the standard group (Group II) of animals. *SP* was administered orally at a dose of 15mg/kg and 35mg/kg body weight to Group -III and Group IV respectively. Rectal temperature was recorded by clinical thermometer at 0, 1, 2, 3 hrs after drug administration and results were tabulated and evaluated by comparing the initial rectal temperature (°C) before yeast injection, with rectal temperature (°C) after 18 hours of yeast injection at different times intervals.

RESULTS

The results of the Antipyretic effect of the various doses of the *SP* (15mg/kg, 35mg/kg), and standard (Paracetamol, 150mg/kg) are depicted in [Table 1 and Fig. 5]. Standard drug and as well as SP at doses of 15mg/kg, and 35mg/kg started showing antipyretic activity after 1 hour of post-dosing. The intraperitoneal injection of brewer's yeast suspension markedly elevated the rectal temperature after 18 hours of administration. Treatment with *SP* at a dose of 15, 35mg/kg decreased the rectal temperature of the rats in a dose-dependent manner. It was found at a dose of 35mg/kg caused significant ($p<0.05$) lowering of rectal temperature at 3 hours following its administration. Whereas the maximum effect was disclosed at a dose of 35mg/kg. The antipyretic effect started as early as 1st hour and the effect was maintained for 4 hours, after its administration. The standard drug paracetamol 150mg/kg and tested drug *SP* significantly reduced the yeast-elevated rectal temperature, at the 2nd and 3rd hours compared to the control group.

Table 1: Antipyretic activity of *SP* by Brewer's yeast-induced method in rats

Treatment	Initial Rectal temp °C	Rectal temperature after 18 hours of yeast injection (°C)			
		0 h	1 h	2 h	3 h
Group I - Control (Honey)	36.97±0.27	40.76±0.24	40.16±0.22	40.2±0.1	40.37±0.15
Group II – Paracetamol 150mg/kg	35.5±0.21	40.1±0.22	39.26±0.23	38.2±0.21	36.12±0.21*
Group III – *SP* 15mg/kg	36.8±0.27	40.35±0.31	39.7±0.32	39.22±0.45	38.32±0.21*
Group IV – *SP* 35mg/kg	36.72±0.4	40.1±0.32	39.8±0.4	38.37±0.38	37.7±0.28*

Values are expressed as Mean ± SEM; Number of animals (n=6). One-way ANOVA followed by a student's unpaired t-test. Results are expressed in mean±SEM. *P<0.05 significant, **P<0.01 very significant, and ***P<0.001 highly significant as compared to control.

Before purification of *Manosilai*

Purification of *Manosilai*

Purified of *Manosilai*

Fig. 1: Purification Process of *Manosilai* (Arsenic di sulphide)

Before Purification of *Milagu*

Purification of *Milagu*

Purified *Milagu*

Fig. 2: Purification Process of *Milagu* (Pepper - *Piper longum*)

Before Purification of *Sangu - Conch*

Purified *Sangu* - Conch

Fig 3: Purification of *Sangu* (Conch – Shell – *Turbinella pyrum L*)

Surangusa Parpam

Fig 4: Trial Drug - *Surangusa Parpam*

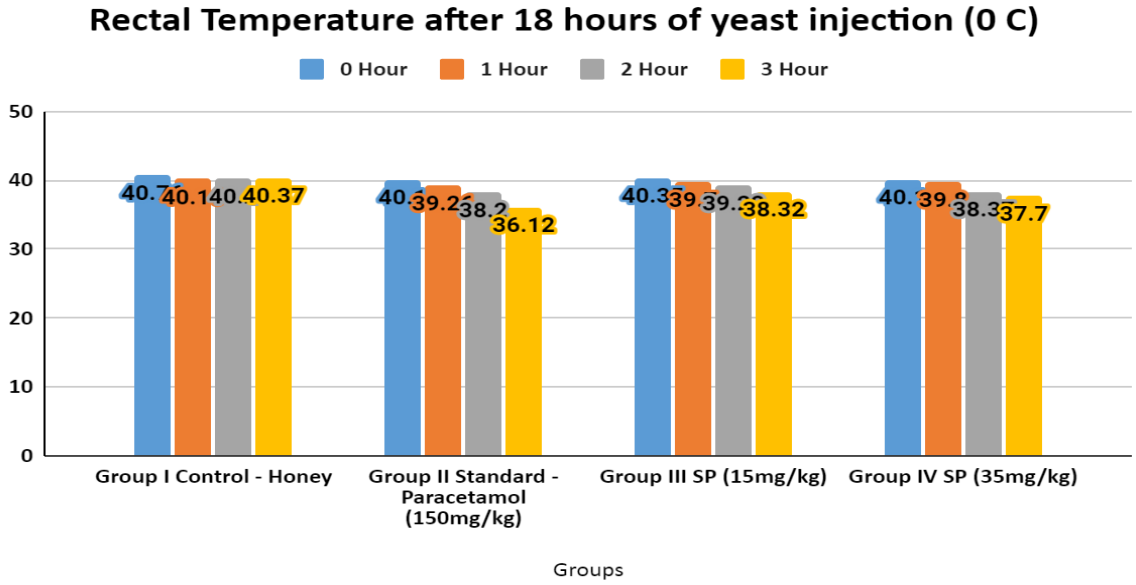

Fig 5: Antipyretic activity of *SP* by Brewer's yeast-induced method in rats – Rectal temperature after 18 hours of yeast injection (^{0}C)

DISCUSSION

This present experiment studied the Antipyretic effect of *SP* on brewer's yeast-induced hyperpyrexia as well as the effectiveness of its antipyretic effect when compared with the standard drug paracetamol. And these antipyretic effects increased with dosage (dose-dependent), it was also seen at higher concentrations (35mg/kg) of *SP.* Fever is known to be caused by several endogenous

pyrogens such as interleukin-1β, interleukin-6, interleukin-8, tumour necrosis factor-α, macrophage protein-1 and prostaglandins. Prostaglandin synthesis may be activated by tumour necrosis factor-α and phospholipase A2. Brewer's yeast induces both TNF-α and prostaglandin synthesis.[14] It is currently accepted that prostaglandin E2 (PGE2) is the final fever mediator in the brain, specifically in the preoptic area of the anterior hypothalamus.[15] Antipyretics such as aspirin (acetylsalicylic acid), paracetamol (acetaminophen) and other non-steroidal anti-inflammatory drugs (NSAIDs) reduce fever by suppressing peripheral production of interleukin-1β, while consecutively lowering the thermoregulatory set point by blocking central cyclo-oxygenase formation of prostaglandin E2. Thus it can be inferred that *SP* inhibits the synthesis of prostaglandins. It has been established that there are two pathways leading to the transcription and induction of cyclo-oxygenase (COX)-2. Both pathways are activated by cytokines e.g. IL-1α, IL-6 and tumour necrosis factor (TNF) which trigger central mechanisms that act via the transcription factors such as nuclear factor (NF) kB and signal transducer and activator of transcription (STAT-3).[16] Both standard and test drugs markedly decreased the rectal temperature of the pyretic rats. This postulation is supported by the antipyretic effect of the *SP* in various doses evidenced by its impact on the pathogenic fever induced by the administration of a yeast injection. Its aetiology includes the production of prostaglandins in the central nervous system, which is the final common pathway for fever induction.[17] Inhibition of prostaglandin synthesis could then be the possible mechanism of antipyretic actions of these *SP.* However, additional studies will be needed to determine if the antipyretic mechanism was due to the inhibition of TNF-β synthesis or prostaglandin synthesis or both.

CONCLUSION

Herbo-mineral medicines have been used for various illnesses for many centuries. Due to better availability, affordable cost, and fewer side effects, they have immense potential. Ingredients of *SP Manosilai* (Arsenic disulphide), *Milagu* (*Piper nigrum*) and *Sangu* (*Turbinella pyrua*) have various medicinal values. Therefore, the present study was planned to evaluate the medicinal properties of herbo-mineral preparation of *SP*. The ingredients of *SP* were found to have various pharmacological actions due to their various constituents. It can be concluded that herbo-mineral preparation *SP* in graded doses (15mg/kg and 35mg/kg) demonstrated significant antipyretic effects on experimental animals in this study.

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