

Anti-inflammatory and analgesic activities of *Vatavidhvamsana rasa*, An Ayurvedic herbo-mineral formulation

Research Article

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Abstract

Background: Inflammation is a complex process mainly comprises of three phases namely acute, sub-acute and chronic. In acute inflammatory conditions fluid and granulocytic cells accumulate at the site of injury because of the changes in small blood vessels. This response often activates systemic response such as leucocytosis, protein catabolism, fever and synthesis of C-reactive protein, an acute-phase protein. In Ayurvedic texts, several herbo-mineral preparations to fight against inflammation have been found; among them, *Vatavidhvamsana Rasa* (VVR) is one, which is said to be remarkable in inflammation condition. **Aim and Objectives:** To assess the anti-inflammatory and analgesic effects of VVR in pharmacologically validated models. **Materials and methods:** Wistar strain albino rats weighing 200 ± 20 of either sex were used in the study. VVR was administered at a dose of 22.5 mg/kg for the rat. **Results:** *Vatavidhvamsana Rasa* (VVR) showed a significant decrease in the carrageenan-induced paw oedema after 1-hour interval in comparison to the control group ($P < 0.05$) and at 3 hours and 5 hours intervals it showed a non-significant decrease in carrageenan-induced paw oedema in albino rats. In the analgesic activity, VVR treated group showed a significant increase in radiant heat response at 30 min. interval ($P < 0.05$) and non-significant increase at 60 mins in comparison to initial and control group. **Conclusion:** The results concluded that *Vatavidhvamsana Rasa* has anti-inflammatory and analgesic activity. Accordingly, it can be used in the management of pain and inflammatory conditions.

Key Words: Analgesic, Anti-inflammatory, Pain, NSAID, Herbominerals, *Vatavidhvamsana Rasa*.

Introduction

Inflammation, although first characterized by Cornelius Celsus, a physician in first Century Rome, it was Rudolf Virchow, a German physician in the nineteenth century who suggested a link between inflammation and cancer, cardiovascular diseases, diabetes, pulmonary diseases, neurological diseases and other chronic diseases. Scientific researches in the last decades has established these remarks and recognized the molecular basis for many chronic diseases with associated inflammatory responses. (1) Conventional management of inflammation and pain includes varied groups of drugs; of them, Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used anti-inflammatory and analgesic drugs. NSAIDs have the capacity to block the synthesis of prostaglandin and hinder the synthesis of lipoxigenase

and superoxide radical. It also upset neutrophil aggregation and adhesion, cytokine production and cartilage metabolism etc. (2) Anti-inflammatory, analgesic and antipyretic actions are due to a common mechanism, that is, inhibition of COX-2 and COX-1, however, simultaneous inhibition of COX-1 result in unwanted side effects. (3)

In the recent context, contemporary medicines have found cures for many health problems including some infectious diseases that cause sickness and premature death on a large scale. These contemporary drugs offer potent treatment for several common ailments, but they also bring a high risk of adverse reactions, which in some cases become distressing. Accordingly, shortfall of the treatment, it becomes mandatory that one should search for medicaments that can defeat all these peculiarities. In this order, a search has been made through the field of *Ayurveda* for medicines that can execute the requirements. Several preparations to fight inflammation have been found in classical *Ayurvedic* manuals. *Vatavidhvamsana Rasa* is a well-known Ayurvedic herbomineral formulation widely used for various neuromuscular diseases. When analysing the ingredients of VVR, most of the drugs were having *Sophahara* (anti-inflammatory) and *Sulahara* (analgesic) properties as per *Ayurveda*. (4) So

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the formulation may have analgesic and anti-inflammatory properties. The study is planned to revalidate the anti-inflammatory and analgesic activities of the VVR in suitable experimental animal models.

Materials and methods

Test formulation

Vatavidhvamsana Rasa (VVR), is mentioned in Yogaratanakara, written in the 18th century AD which is also quoted in Ayurvedic Formulary of India (AFI). (5) Raw materials were procured from the Pharmacy of Institute and were identified and authenticated by the Pharmacognosy department and faculty of RSBK department of the institute as per the standards of Ayurvedic Pharmacopeia of India. Preparation of *Kajjali* (a combination of Hg and S) is by grinding one part each of processed mercury and processed sulphur using mortar and pestle, till it attains a lusterless black fine powder form. (6) Then one part each of *Maricha* powder (*Piper longum* Linn.), *Naga Bhasma* (processed lead), *Vanga Bhasma* (processed tin), *Tamra Bhasma* (processed copper), *Abhraka Bhasma* (processed mica), *Loha Bhasma* (processed iron), *Tankana* (processed borax), and two parts each of *Pippali* powder (*Piper longum* Linn.), *Shundi* powder (*Zingiber officinale* Roscoe), was added one by one to the *Kajjali* and triturated well using a *Khalvayantra*. After that 4.5 parts of *Shodita Vatsanabha Churna* (*Aconitum Chasmanthum* Staff. Ex.Holmes) was added and triturated well to form a uniform fine mixture. This was triturated three times each of the ten media (Table 1). Then the final product was dried in shade and stored in an airtight glass container.

Table 1: Ingredients of *Vatavidhvamsana Rasa*

No	Ingredients	Parts	Media for levigation
1	<i>Shodita Parada</i>	1 part	Three times triturated in each of the following drugs
2	<i>Shodita Gandaka</i>	1 part	1. Decoction of <i>Trikatu</i>
3	<i>Vanga Bhasma</i>	1 part	2. Decoction of <i>Triphala</i>
4	<i>Naga Bhasma</i>	1 part	3. Decoction of <i>Plumbago zeylanica</i> Linn.
5	<i>Tamra Bhasma</i>	1 part	4. Juice of <i>Eclipta alba</i>
6	<i>Loha Bhasma</i>	1 part	Hassk.
7	<i>Abhraka Bhasma</i>	1 part	5. Decoction of <i>Saussurea lappa</i> C.B.Clarke
8	<i>Shodita Tankana</i>	1 part	6. Juice of <i>Vitex negundo</i> Linn.
9	<i>Pippali</i>	2 part	7. Latex of <i>Arka</i>
10	<i>Shunthi</i>	2 part	8. Juice of <i>Bhumiamalaki</i>
11	<i>Maricha</i>	1 Part	9. Decoction of <i>Lepidium sativum</i> Linn
12	<i>Shodita Vatsanabha</i>	4 ½ Parts	10. Juice of <i>Citrus lemon</i>

Animals

Wistar strain albino rats of either sex weighing 200 ± 20 g were obtained from the animal house attached to the pharmacology laboratory attached to the Institute. The animals were given potable water ad libitum and given 'Amrut' brand animal pellet feed (manufactured by Pranav Agro Industries). The animals were kept in optimum temperature and humidity and they were allowed for natural day-night cycles. The

experiments were carried out in conformity with the guidelines of the Institutional Animal Ethics Committee after obtaining its permission (approval number IAEC/24/2018/21) and care was taken as per Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

Dose fixation

The dose of the test formulation of rats was fixed by using table of Paget and Barnes. (7) Thus the adult human dose of test drug VVR (250 mg per day) was converted to rat dose on the basis of body surface area ratio as per the table (22.5 mg/kg p.o). The test drug was suspended in distilled water by making a uniform suspension with honey with suitable concentration depending upon the bodyweight of the animals and administered orally with the help of a gastric catheter connected to a syringe. The drug was administered to overnight-fasted animals.

Experimental protocols

Anti-inflammatory activity Carrageenan-induced paw oedema in rats (8)

The Wistar strain albino rats of either sex were weighed and randomly, divided into three groups of six each. The first group (control group) received potable water. The second group received the test drug, *Vatavidhvamsana Rasa* (VVR) and the third group was administered with standard anti-inflammatory drug phenylbutazone (model 520, IITC Life Science Inc.) at a dose of 100 mg/kg. (9) The test drug was administered to the second group for five consecutive days, whereas the standard drug was given only once on the fifth day, one hour before the carrageenan injection. The left hind paw volumes up to the tibiotarsal articulation was recorded before the carrageenan injection by using a plethysmograph. (10,11) After one hour of drug administration, oedema was produced by injecting 0.1 ml freshly prepared 1% w/v carrageenan in sterile saline solution to the sub-plantar aponeurosis of the left hind limb of the rat. The animals were given potable water in 2 ml/100 g body weight to ensure proper hydration. This in turn helps to reduce the variations in oedema produced. The intensity of oedema formation over paw was recorded after one, three and five hours of carrageenan injection. The results obtained after one, three and five hours were stated as the percentage increase in paw volume compared to the initial values of paw volume.

Analgesic activity radiant heat-induced pain by hot plate method (12)

A heat-conductive surface, such as metal, is heated to a temperature that will induce a nociceptive response in an animal subject normally 50-56°C. The animal is then placed onto the surface and prevented from leaving the platform by blockades. The latency to pain-reflex behaviour is measured. This model executes the effect of test drug on the latency of paw licking or jump response, which represents pain threshold, was measured in rats employing the procedure of

incremental hot plate. In this experiment, the paw licking or jump response was observed by the IITC incremental Hot plate. The IITC incremental Hot plate is designed to enable the operator a more precise reading of thresholds due to temperature than the standard constant temperature hot plates used for latencies. When the animal reacts to the heat the test is stopped and the plate will automatically be cooled to the user set standby temperature. The Wistar albino rats weighing between 200±20 g of both sex were randomly selected and distributed in three groups of six each.

The first group served as the control group received potable water. The second group received the test drug, *Vatavidhvamsana Rasa* (VVR, 22.5 mg/kg p.o.). The third group was administered the standard analgesic drug Pentazocine (20 mg/kg, p.o.). The effect of the test drug on the latency of paw licking or jump response, which represents pain threshold, was measured in rats employing the procedure of incremental hot plate. The animals were positioned on an incremental Hot plate kept at a temperature of 55±0.5°C. A cut off period of 15 sec was observed to avoid damage to the paw. (13) The initial reading was noted for each rat for paw licking or jump response. The test drugs were administered to respective groups and distilled water to the control group. The latency of onset of reaction time was again recorded at 30, 60, 120, 180 and 240 min after the administration of the drug. (14,15)

Statistical Analysis

The obtained results were presented as Mean ± SEM. The data generated during the study were subjected to Student Paired and Unpaired ‘t’ test, as well as one way ANOVA, followed by Dunnett’s multiple ‘t’ test as post-hoc test applicable. A value of P<0.05 was considered to be significant.

Results

The result shows that *Vatavidhvamsana Rasa* showed a significant decrease in the carrageenan-induced paw oedema (P< 0.01) after 1-hour interval in comparison to the control group (P<0.05) and at 3 hours and 5 hours intervals it showed a non-significant decrease in carrageenan-induced paw oedema in albino rats. Phenyl butazone treated group showed a highly significant decrease in carrageenan-induced paw oedema after 1 hour and 5 hours when compared to the control group (Table 2). The data related to the effect of test drugs on radiant heat-induced pain through the hot plate model at different intervals in rats are tabulated in Table 3. The normal control group showed a non-significant decrease in response to radiant heat at all-time intervals. VVR treated group showed a significant increase in radiant heat response at 30 min. interval and non-significant increase at 60 minutes in comparison to initial and control group. Pentazocine treated group showed a highly significant increase in radiant heat response at all-time intervals compared to the control group as well as initial readings.

Table 2: Effect of test drugs on carrageenan-induced paw oedema in albino rats

Groups	% Increase in paw oedema at different time interval		
	After 1h	After 3h	After 5h
NC	33.58±3.38	44.12±8.79	62.01±3.36
VVR	21.78± 1.94* [@]	35.64±5.58	47.95±9.81
SC	15.22±2.06*** ^{@@}	32.58±2.77	33.58±3.38*** [@]

NC- Normal control, SC-Standard control, VVR- *Vatavidhvamsana Rasa*, Data: Mean±SEM; *P<0.05, **P<0.01, ***P<0.001 compared to normal control group (Unpaired ‘t’ test); [@]P<0.05, ^{@@}P<0.01 compared to normal control group (Annova followed by Dunnett's multiple ‘t’ test)

Table 3: Effect of test drugs on radiant heat response in albino rats

Oral treatment (mg/Kg)	Latent period					
	Initial	30 min.	60 min.	120 min.	180 min.	240 min.
NC	3.28±0.11	3.17±0.11	3.09±0.14	2.92±0.19	3.09±0.25	3.01±0.43
VVR	2.90±0.17	3.44±0.08*	3.13±0.42	2.63±0.21	2.59±0.19	2.38±0.36
SC	3.02±0.12	5.05±0.43* ^{@@}	5.43±0.28*** ^{@@}	6.24±0.63*** ^{@@}	5.29±0.40*** ^{@@}	4.90±0.36*** [@]

Discussion

Inflammation is a complex process mainly comprises of three phases namely acute, sub-acute and chronic. In acute inflammation, due to change in small blood vessels, fluid and granulocytic cells accumulate at the site of injury. This response often activates a systemic response such as leucocytosis, protein catabolism, fever and synthesis of C-reactive protein, an acute-phase protein. (16) In conditions where inflammation is inappropriate, acute inflammation can cause considerable morbidity hence drugs with anti-inflammatory activity would be required to meet the contingencies in such situations. The test formulation

was evaluated against carrageenan and formaldehyde induced acute paw oedema to assess its effect on acute inflammation and cotton pellet induced granuloma formation to assess its effect on chronic inflammation. Carrageenan induced rat paw oedema has been a popular inflammatory model to investigate the anti-inflammatory potency of compounds or natural products. A high degree of reproducibility was exhibited by this experimental model. (17) According to Vinegar et al (1969), a carrageenan-induced paw oedema is a biphasic event. The first phase of reaction was generated within one hour and is attributed to the release of histamine, serotonin and kinins and partly due to the trauma produced by injection. The second phase

of oedema is due to the release of prostaglandins (PG), protease and lysosome. Most of the clinically effective anti-inflammatory drugs are effective in the second phase. Prostaglandins play a major role in the development of the second phase of the reaction, which is measured around 3 h. The presence of PGE₂ in the inflammatory exudates from the injected foot paw can be demonstrated at 3 h and thereafter. (18) The present study revealed that the test drug suppresses carrageenan-induced paw oedema in the initial phase which is statistically significant when compared to normal control while after 3 and 5 hours it shows a statistically non-significant decrease. Thus, the drug is very effective in the early stages of inflammation and might stop the release of histamine, serotonin and kinins and in the late phase also showed noticeable suppression in oedema in albino rats. "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage" this is a definition given by IASP (International Association for the Study of Pain). (19) Pain-relieving drugs act on peripheral or CNS to selectively reduce pain without altering consciousness. (20)

The animal model employed for screening analgesic activity in this study is the pain-state model using thermal stimuli which include the hot plate method. This method is useful in illustrating centrally mediated ant nociceptive responses which focus generally on changes above the spinal cord level. (21) Hot plate strategy includes higher brain capacities and is respected as a supraspinally organized reaction. (22) In this show, tactile nerves sensitize the nociceptors and the association of endogenous substances such as prostaglandins are minimized. (23) VVR treated group showed a significant increase in radiant heat response at 30 minutes interval but no significant changes at other intervals in comparison to the initial as well as the control group. Pentazocine treated group showed significant analgesic activity in radiant heat response at all-time intervals compared to the control group as well as initial readings. The hot plate model, which is thermal-induced nociception, indicates narcotic involvement, which is sensitive to opioid receptors. Pain is centrally modulated via several complex processes including opiate, dopaminergic descending noradrenergic and serotonergic systems. (24) The mild to moderate increase in pain threshold produced by test drug in early phase at 30 mins interval in this model, suggests the involvement of central pain pathways. The analgesic effect produced by VVR and standard drug in the early phase possibly will be through central mechanisms (by receptor systems) or through peripheral mechanisms like inhibiting the release of prostaglandins, leukotrienes, and other endogenous substances. Glycosides, Flavonoids and tannins present in the plant extract may be responsible for the analgesic activity because it is well established that a wide range of bioactivities is dependable to these phytochemicals. (25)

As mentioned earlier, *Vatavidhvamsana Rasa* contains metals and minerals like Mercury, Sulphur, Lead, Tin, Copper, Iron, Mica, and *Aconitum*

Chasmanthum Staff. Ex.Holmes. It is indicated for *Sula* (pain), *Vatakapha* diseases, *Grahani* (Irritable bowel syndrome), *Sootika rogas* (Post-partum pain syndromes), *Apasmara* (epilepsy). The main ingredient, *Vatsanabha* is having *Sulahara* (analgesic) and *Yogavahi* (catalyst) property. (26) *Vatsanabha* is also indicated in different conditions like *Gridhrasi* (sciatica), *Katisoola* (low backache), *Sirasula* (Headache) etc. Certain drugs like *Chitraka*, *Kushta*, *Chandrsoora*, *Nirgundi* and *Trikatu* are known to be having *Sulahara* (analgesic) property. (27-31) Altogether while we analyze the combination it is a very good analgesic drug. The indications described point out the fact that this combination of *Vatavidhvamsana Rasa* is effective in musculoskeletal, post-traumatic/surgical and visceral pain. These properties may be given in revealing anti-inflammatory and analgesic activities of the VVR.

Conclusion

The study validated the claim for the use of *Vatavidhvamsana rasa* in inflammation and pain Accordingly, it can be used in the management of pain and inflammatory conditions.

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