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Original Article
In vivo studies

Comparative Antipyretic Effect of *Nagaradi Kwatha, Ghana Vati* and *Arishta* in Wistar Albino Rats

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ABSTRACT

Introduction: *Kwatha* (Decoction) *kalpana* is one amongst the basic preparations in herbal pharmaceutics. Marketing these formulations is not possible because of its shorter shelf life and hence *Nagaradi Kwatha* is converted to *Arishta* (fermented product of decoction) and *Ghana vati* (solidified aqueous extract) form by using the method of *Anukta paribhasha* explained in the classical texts of Ayurveda. *Nagaradi Kwatha* is widely used in clinical practice as *Jwaraghna* (antipyretic). *Nagara, Haritaki* and *Guduchi* are the main ingredients, which helps in *ama pachana* here by relieves *Jwara* (fever). ***Methods***: The pyrexia was induced by subcutaneous injection of 20% of Brewer's yeast solution at a dose of 1ml/100g body weight. The group specific drugs were administered after 18th hour of yeast injection. The rectal temperatures were recorded by using digital Telethermometer before yeast injection and at hourly interval for 4 hours, 24 h after the yeast injection. ***Results***: The results are significant indicators of the anti-pyretic activity of *Nagaradi* combination. The *Arishta* form of *Nagaradi* combination was significantly decreased the rectal temperature measured at 1st, 3rd, 4th and 24h after fever induction. ***Conclusion***: It can be concluded that the *Arishta* form has better antipyretic effect than *Kwatha and Ghana vati* form of *Nagaradi* combination.

KEYWORDS

Antipyretic, *Nagaradi Arishta, Nagaradi Ghana vati*, *Nagaradi Kwatha,* Brewer's yeast.

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Fever is a complex physiologic response triggered by infectious conditions such as urinary tract infections, meningitis, malaria common cold, and appendicitis or non infectious causes such as vasculitis, deep vein thrombosis. Increase of body temperature in febrile condition is regarded as a component of the complex host response to infection or inflammation that accompanies the activation of the immune system.[1] Late phases of fever appear mediated by pro-inflammatory cytokines called endogenous pyrogens. Elevations in body temperature occur when concentrations of prostaglandin E2 (PGE-2) increase within certain areas of the brain.[2] These elevations alter the firing rate of neurons that control thermoregulation in the hypothalamus. According to Acharya Charaka *jwara* (fever) is the *santhapa* of body, mind and *indriyas* (sense organs). Due to *mithya aharavihara jataragni* (normal functioning of gastrointestinal tract) functions are impaired leading to *ama*. Thus the *Ama* is the main cause for *jwara*.[3]
The *Nagaradi Kwatha*[4] found in Sahasrayoga in the context of *Jwara Chikitsa* contains the ingredients as drugs *guduchi (Tinospora Cordifolia), hareetaki(Terminalia Chebula)* and *shunti* (*Zingiber officinale*) posses main property like *deepana shrotoshodana* and *agnimandya nashaka* respectively.[5] Many research works carried out in this direction with single herb with *Guduchi* showing the anti pyretic effect in experimental study.[6]
The selection of *Kashaya kalpanas* for treatment purpose depends on various factors like *roga, rogibala, desha, kala, agni and vaya.*[7] *Panchavidha kashaya kalpanas* are the basic pharmaceutical preparation and most important form of *kalpanas*. These *kalpanas* cannot be preserved for longer duration. Among these, *Kwatha* can be preserved for 3 hours.[8] Due to the advent of commercialization longer shelf life has become the need of hour, especially for the preparation of *Kwatha* (Decoction) which are highly perishable. *Nagaradi Kwatha* is one of the routinely practiced yoga in *jwara* which helps in the *samprapti vighatana.* Which contains *Nagara, Haritaki* and *Guduchi* as the ingredients in the ratio of 3:2:1 is commonly used in the form of decoction for fever in clinical practice. These *Kwathas* are available in market with preservatives and also in form of tablets prepared with the addition of different additives. Even though preservatives and additives are considered to be inert, one cannot expect the same result as that of freshly prepared *Kwatha*. Converting *Kwatha* into different dosage forms like *Ghana vati,* (solidified aqueous extract) *Arishta* (Self generated alcoholic liquid) may help to increase the shelf life without much change in the property of the particular formulation[9]. Here *Nagaradi Kwatha* is converted into *Nagaradi Arishta* and *Nagaradi Ghana vati* by following the method of *anuktha mana* and *anuktha paribasha* respectively.[10, 11] However, *jwarahara* (Antipyretic) property of this formulation has not been reported till date. Considering this, study was undertaken to evaluate comparative anti-pyretic efficacy of *Nagaradi Kwatha, Ghana vati* and *Arishta* in experimental animals.

MATERIALS AND METHODS

Procurement and preparation of test drug

The raw materials i.e. *Haritaki, Shunti* and *Guduchi* were collected and authenticated from the S.D.M. pharmacy, Udupi, Karnataka, India. To prepare *Nagaradi Kwatha Guduchi, Shunti, Haritaki* are taken in the ratio of 3;2;1 respectively, boiled and reduced to 1/8th subjected to filtration. The same *Kwatha* is used for the preparation of *Ghana vati* by reboiling the *Kwatha* till it attains semisolid state, such paste is rolled into pills form of 500mg which further on drying shall be divided into ten equal parts of 45mg each and used for the study. The same prepared *Kwatha* is used for the preparation of *Arishta* by adding jaggery, Honey, *Prakshepaka* (powders of ingredents) and Dhataki pushapa by following *Anukta mana* of Sharanghadara Samhita and left for formentaton for the period of 45 days.

Dose selection and administration of the trial drug

The dose of *Nagaradi Kwatha* and *Arishta* for antipyretic effect in human is 48ml [12,13]. Whereas the *Ganavati* form of test drug is 500mg. [11] The dose of experimental animals was calculated by extrapolating the human dose to animal dose based on body surface area ratio by referring to the standard table of Paget and Barnes (1964). [14] On this basis, the rat dose of *Kwatha* and *Arishta* was found to be 4.32 ml / kg body weight. The test drug was administered orally to animals with the help of oral catheter. The Trial drug *Nagaradi Ganavati* was administered at a dose of 45 mg / kg body weight by making small micro pellet administered with the help of oral catheter.

Experimental animals

Wistar albino rats (180-250g) of either sex were procured from Animal House attached to Pharmacology laboratory at SDM Centre for Research in Ayurveda and Allied Sciences, Udupi, Karnataka. The animals were kept under standard environmental conditions of room temperature (23 ± 2°C), relative humidity (55% ± 5%). The animals were housed in the colony cages (6 rats per cage). The animals were fed with rat pellet (Pranav Agro Ltd' "*Amrut*" brand rat pellet) and water *ad libitum*. The institutional animal ethics committee was approved experimental protocol with the reference number (CPCSEA/2011-RS01). Six animals per group were used in each experiment. The animals were fasted for 18 hours before the commencement of the experiment but allowed free access to drinking water. All the experiments were carried out in accordance with the guidelines of Institutional Animal Ethics Committee.

Study design

Animals were kept under fasting for 18 hours before the commencement of the experiment. Initial rectal temperatures of all the animals were recorded by digital Tele thermometer. The pyrexia was induced by subcutaneous injection of 20% of Brewer's yeast solution at a dose of 1ml/100g body weight [15]. The group specific drugs were administered after 18th hour of yeast injection. Group I rats were administered with distilled water 1ml /kg body weight and served as normal control. Group II rats were administered with paracetamol 100mg / kg body weight and served as reference standard. Group III, IV & V rats were administered with the *Nagaradi Kwatha, Ghana vati* & *Arishta* respectively. The rectal temperatures were recorded by using digital telethermometer before and after fever induction and at hourly interval for initial 4 hours followed by 24 h after the yeast injection.

Statistical Analysis

The data was expressed as Mean ± SEM and analyzed by one way ANOVA followed by Dunnet's multiple comparison t-test using Graph Pad Prism 3. A $p < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Paracetamol showed significant ($p<0.01$) antipyretic effect during 2nd and 4th h after drug administration, whereas the *Arista* form of test drug showed significant antipyretic effect at 1st , 3rd & 4th hour after drug administration ($p<0.01$). The *Ganavati* and *Kwatha* form of test drug was significantly reduced rectal temperature measured during 1st & 24th h and 2nd & 4th h respectively after drug administration (Table 1).

Nagaradi Kwatha is classically used for generalized fever and the use is well established in *Ayurvedic* practice. The present study is mainly focused on the effect of different dosage forms of the *Nagaradi dravya* combination such as *Kwatha, Ganavati, and Arishta* for their anti pyretic effect. Brewer's yeast is a fungi containing lipo-polysaccharide, which is a cell wall component of gram negative bacteria. It binds with macrophages and releases cytokines, interleukin - 1 etc into the blood circulation, leading to antigen-antibody reaction. Then it crosses blood brain barrier and releases arachidonic acid mediated by the enzymes phospholipase, prostaglandin E2 synthase, and cyclo-oxygenase. The synthesis and release of PGE2 into anterior hypothalamus results in pyrexia. [16,17] In the present study the pyrexia was induced by subcutaneous injection of 20% Baker's yeast at a dose of ml/100g body weight and the rats with rectal temperature above the basal temperature was recruited for the study. The Pyrexia was achieved after 18h after yeast injection. Later the test drugs and vehicle to control group were administered by oral route with the help of syringes attached with oral catheter. There after the rectal temperature was measured repeatedly at an interval of 1st, 2nd, 3rd, 4th, and 24th h. The present study was mainly focused on the short term evidence and of antipyretic activity of the test formulations and hence the rectal temperature was measured at initial four consecutive hours followed by 24h time intervals.

The rectal temperatures of control group rats were continuously raining throughout the experimental period. The standard drug paracetamol administered rats showed remarkable reduction in the rectal temperature during 2nd, 3rd and 4th h of reading and found to be statistically significant in comparison to control group rats. Similar pattern of hourly reduction in temperature is

seen in *Kwatha* group. The test drug *Arishta* form has found to be highly effective and decreased the rectal temperature significantly in comparison to control group rats. The analysis of the results obtained clearly indicates that all the test group drugs have significant anti-pyretic activity. Comparison among the test formulations revealed that *Arishta* form of test drug has significant ($p<0.01$) anti-pyretic activity. In fact *Kwatha* and *Ghana vati* group produced moderate and statistically significant reduction in the rectal temperature followed by injection of yeast suspension.

Table 1. Effect of test drugs on rectal temperature (^{0}C) at different time interval in Brewer's yeast induced pyrexia in experimental animals

Group	Initial	After 18h of yeast injection	1h	2h	3h	4h	24h
Pyretic control	37.91± 0.04	38.18± 0.29	39.03±0.10	39.26 ± 0.12	38.75 ± 0.22	38.95 ± 0.15	37.58 ± 0.19
Paracetamol	37.90± 0.22	38.95± 0.07	38.65±0.16	38.01 ± 0.24**	38.71 ± 0.13	38.33± 0.20*	37.85 ± 0.20
Kwatha	37.95± 0.16	38.93± 0.06	38.86±0.11	38.10± 0.10**	37.71 ± 0.17	38.26 ± 0.14*	37.51 ± 0.16
Ghana vati	37.98± 0.19	38.68± 0.13	38.45 ±0.20*	38.66 ± 0.15	38.65 ± 0.14	38.58 ± 0.11	37.53± 0.14**
Arishta	37.23± 0.09	38.73± 0.14	38.2 ±0.073**	38.66 ± 0.31	37.83± 0.21**	37.6± 0.13**	38.41 ± 0.21

Data expressed in Mean ± SEM, *P<0.05, **P<0.01 in comparison to normal control.

On the basis of present the study *Arishta* form showed significant effect compared to other dosage forms, even when it is compared with standard drug. It may be due to the qualities of self generated alcohol better known by the term *Madya guna* attributed to the *Nagardi yoga* by the *samskaras* during *Arishta* preparation. *Madya gunas* like *saukshmya* (enter in to minute pores), *teekshna* (cleans the channels of the body), *vyavaayi gunas* (drugs that spread throughout the body without first getting digested), *ushna* (hot), *laghu* (light) help in the faster absorption of the drug, which in turn increases its efficacy. [18] This may be the reasons for the better anti-pyretic activity profile in *Arishta* form of *Nagaradi yoga* when compared to *Kwatha* and *Ghana vati* . *Ghana vati* on the other hand is a solid dosage form, where as *Arishta* and *Kwatha* are liquid dosage forms. While considering the mode of drug action, liquid dosage form is likely to have faster absorption than solid dosage forms. Here for *Ghana vati,* experimental results showed significance in 24th hr reading than the readings in the initial hours. This delayed action may be due to longer the disintegration time (2 hours) taken by the vati (solid dosage form).

Paracetamol (Acetaminophen) is generally considered to be a weak inhibitor of the synthesis of prostaglandins (PGs) in the peripheral tissues, but more active on cyclo-oxygenase in the brain. However, the in vivo effects of Paracetamol are similar to those of the selective cyclooxygenase-2 (COX-2) inhibitors. Paracetamol also decreases PG concentrations in vivo, but, unlike the selective COX-2 inhibitors. The *Nagaradi* combination has shown significant anti-pyretic activity and the probable mechanism of action may be as follows. Among the likely mechanisms is inhibition of formation of endogenous pro-inflammatory molecules like PGE and cytokines; or blocking of their receptors. The drug may also act by down regulating the thermoregulatory circuits or by enhancing the formation and release of endogenous anti-pyretic factors enumerated above.

CONCLUSION

From the present study, it can be concluded that the *Arishta* form of *Nagaradi* combination has high degree of antipyretic action as compared to *Kwatha* and *Ganavati*. The antipyretic effect of *Arishta* form of *Nagaradi* combination was comparable with that of reference standard paracetamol. Thus the study provides evidence for the presence of anti-pyretic activity in the *Nagaradi* combination in the *Arishta* form. The specific reason behind the formulation is need to explore in the further experimental model.

CONFLICTS OF INTEREST

Nil

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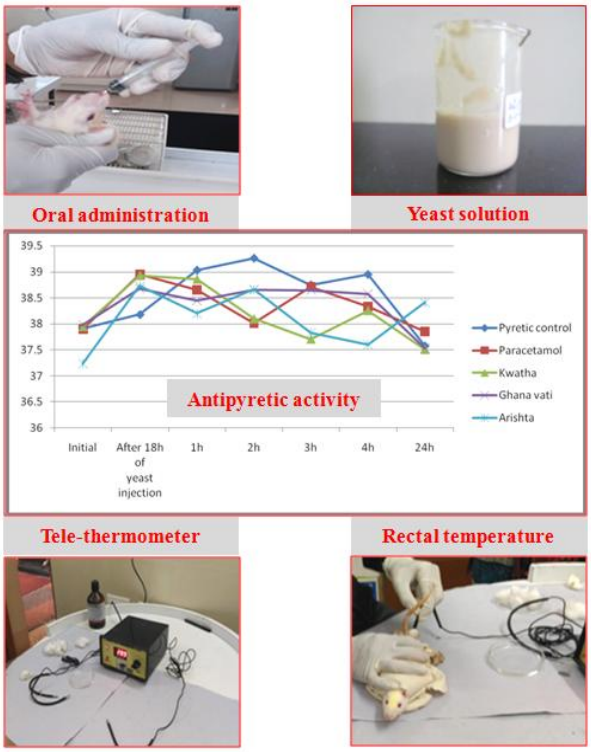
GRAPHICAL ABSTRACT



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