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Preclinical Pharmacological Assessment of *Tribhuvana-Mishrana* (TM) and its Ingredients

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ABSTRACT

Objective: The present pharmacological investigation was undertaken to study the anti-pyretic activity of *Tribhuvana-Mishrana*(TM) and its ingredients viz. *Tribhuvanakirti Rasa* (TKR), *GodantiBhasma*(GB) and *Sudarshana Ghana Vati*(SGV).

Material and Methods: Antipyretic study of *Tribhuvana-Mishrana*and its ingredients were carried out on 36 Wister Albino rats against yeast induced pyrexia of both Sex. Six groups of six animals were used for the experiment. The yeast induced pyrexia method was standardized first by injecting subcutaneously 20 % w/v of brewer's yeast (10ml/kg) in distilled water followed by recording the rectal temperature at regular intervals. Then the evaluation of anti-pyretic activity of *Tribhuvana-Mishrana* and its ingredientswere carried outby using this standard procedure.

Results:*Tribhuvana-Mishrana* and its ingredients attenuated the raise in temperature after two hours of yeast injection. After 4 hr. of yeast injection also *Tribhuvana-Mishrana* and its ingredients attenuated the raise in temperature in a highly significant manner in comparison to both control and standard groups. The data generated during study shows that *Tribhuvana-Mishrana* and its ingredients having significant anti-pyretic activity.

KEYWORDS

Tribhuvana-Mishrana, Brewer's Yeastpyrexia, Safety, Paracetamol, Herbometalic Formulation.

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INTRODUCTION

Jwara (fever /hyperpyrexia) is considered among the first disease ailing to human beings[1], as it takes away the life of all living beings and causes *santapa* in both body and mind. No other disease is as severe, complicated and difficult for management as *jwara*[2]. According to modern science, fever is a surrogate marker for disease activity in many infectious and inflammatory disorders. In fact fever is one of the commonest symptom which is experienced by every individual at least ones in a life and whenever persons suffers from fever it is the common practice to take antipyretic medicines such as *Paracetamol, Nimusulide, Diclofenac Sodium* etc. but these medicines are having various side effects like dyspepsia, ulceration, GIT bleeding, rashes, epigastric distress, heart burn, pruritis, etc. To avoid these side effects the physicians are need of a safe and effective antipyretic medicine. There are many single drugs and formulations prescribed for *jwara* in our classics like *churna, vati* to *herbomineral* preparations. *Bhasma*and *Rasoushadhies* are found very potent in eliminating dreadful diseases and also for rejuvenation purpose due to their innate qualities like quick action, lesser dose, tastelessness, prolonged self-life, and better palatability[3]. *Tribhuvanakirti Rasa, GodantiBhasma and Sudarshana Ghana Vati* are separately indicated for the treatment of *Jwara* in different dosage forms.

Tribhuvana-Mishrana is an important *Rasa yoga (*herbo-metallic preparation) which is described in AFI Part III (*Rasa yoga* Group 15), published by Dept. of AYUSH, Govt. of India. It is the combination of three different types of *Ayurvedic* medicines:**i)***Tribhuvanakirti Rasa* (1 part), **ii)***GodantiBhasma*(1 part) and **iii)***Sudarshana Ghana Vati*(2 part). It is anubhuta yoga (CGHS formulary) used in *Sannipata*(vitiation of all doshas/severe condition of any disease), *SarvaJwara* (all types of fever) and *Pratishyaya* (coryza).It is given in dose 125-250 mg twice daily with Luke warm water and ginger juice.Purified Cinnabar (HgS),the chief ore of Mercury is one of the ingredients of *TribhuvanaMishrana*.

MATERIALS AND METHODS

1. Preparation of drug

As far as this study is concerned, the trial drug of *TribhuvanaMishrana* was prepared in powder form as follows: -

*Tribhuvanakirti Rasa*as per A.F.I. specifications[4]

GodantiBhasma as per *Rasamritam*[5]*Sudarshana Ghana Vati* as per

A.F.I. specifications[6] *Tribhuvana Mishrana*as per A.F.I. specifications[7]

2. Selection of raw materials

All the ingredients were procured from the Khari Baowli Market, Old Delhi, India except leaves of *Nimba, Dronapushpi, Tulasi, Dhatura, Nirgundi*were collected from Rajaji national park Shyampur, Haridwar, Uttarakhand, India and rhizome of *Adraka*collected from local market of Haridwar authenticated by subject expert. For preparing *TribhuvanaMishrana*, processing were carried out in Department of *Rasa Shastra and BhaishjyaKalpana*,UttarakhandAyurved University, Rishikul Campus, Haridwar, Uttarakhand, India.

The detail planning of experimental study as well as the results and observations of the study were documented and analyzed statistically. This experimental study was carried out at 'Institute of Biomedical and Industrial Research', Jaipur, Rajasthan after obtaining permission from Institutional Animal Ethics Committee with Approval no. ibir/iaec/2015/II/4.

Anti Pyretic Activity

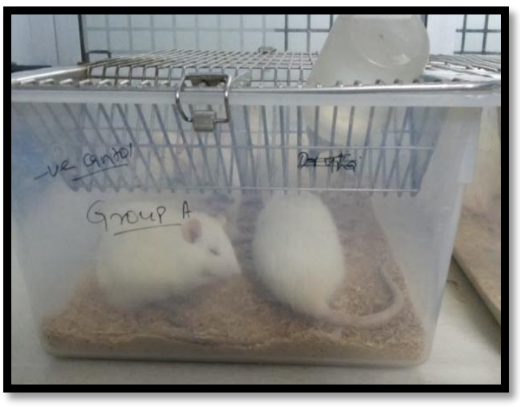
Yeast induce Pyrexia in Rats

Preparation of animals

The animals were randomly selected, marked with Picric acid H (Mark on head), B (Mark on Back), T (Mark on Tail), HT (Mark on head and Tail), HB (mark on head and Back), BT (Mark on tail and Back) for individual identification, and kept in their cages for at least 5 days prior to dosing to allow for acclimatization to the laboratory conditions. Indusial rat had been marked with picric acid

Number of animals and dose levels

Thirty six animals were used for each group. Each Group had 6 rats. In group A (Induced Control) ~~had~~ 6 Pyrexia Induced rats ~~and~~ were administered ~~with~~ distilled water 5 ml/kg per oral.Group B had 6 Pyrexia Induced rats and were administered with *GodantiBhasma* 90 mg/kg per oral.Group C had 6 Pyrexia Induced rats and were administered with*Tribhuvankirti Rasa* 90 mg/kg per oral.Group D had 6 Pyrexia Induced rats and were administered with *Sudarshan Ghana Vati* 90 mg/kg per oral.Group E had 6 Pyrexia Induced rats and were administered with *Tribhuvan-Mishrana* 90 mg/kg per oral.Group F (Standard) had 6 Pyrexia Induced rats and were administered with Standard Drug Paracetamol 50 mg/kg per oral. (Figure 1)

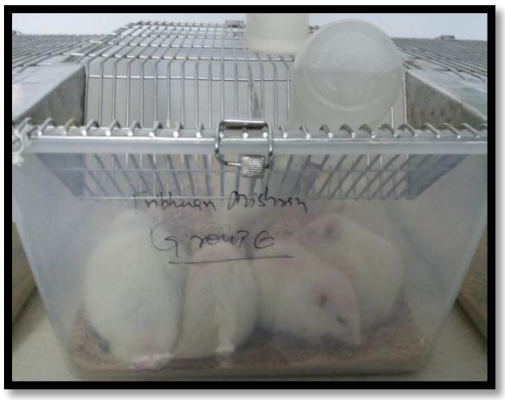


Group –A (induced control)

Group –B (*GodantiBhasma*)

Group –C (*Tribhuvanakirti Rasa*)

Group –D (*Sudarshana Ghana Vati*)



Group –E (*TribhuvanaMishrana*)

Standard Group (Paracetamol)

Figure 1 Anti Pyretic Activity of Tribhuvana-Mishrana (TM) and its ingredients on Yeast induced Pyrexia in albino Rats

Inducing Pyrexia

Pyrexia was induced by subcutaneous injection of 20 % w/v of Brewer's Yeast (10ml/kg) in distilled water (Figure 2). Basal rectal temperature was measured before the injection of yeast, by inserting digital thermometer to a depth of 2 cm into the rectum. The rise in rectal temperature was recorded 18hr after yeast injection.

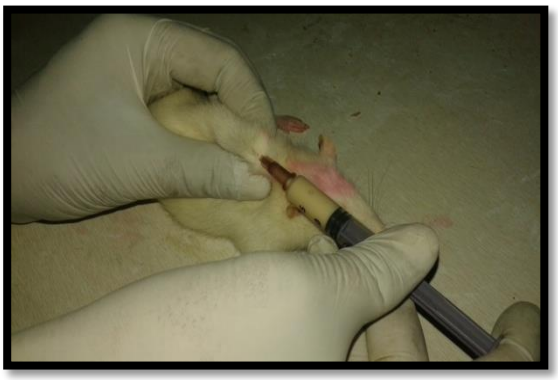


Figure 2 Administration of yeast

Administration of doses (Figure 3)

Calculated dose was administered orally with help of oral fiddling needle after inducing pyrexia.

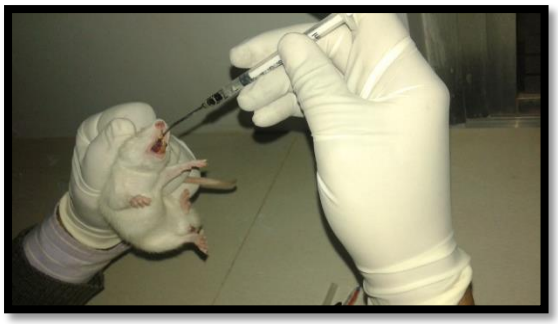


Figure 3 Administration of trial drug

Statistical analysis-

The results were expressed as Mean ± SEM Comparison between each hr and each group were performed by analysis of variance (ANOVA). In all tests the criterion for statistical significance was P < 0.05 (table 1, table 2)

RESULTS

Table 1 Mean and standard deviation of rectal temperature in albino rats at different hours

Test group	B.T.(X±SD)	18hr after yeast administration (X±SD)	1hr (X±SD)	2hr (X±SD)	3hr (X±SD)	4hr(X±SD)
Group A (induced control)	36.25±0.27	38.30±1.12	38.53±0.79	38.52±0.66	38.65±0.63	38.55±0.44
Group B (*GodantiBhasma*)	36.03±0.47	38.58±0.48	38.90±0.69	38.83±0.70	38.27±0.43	37.73±0.53
Group C (*Tribhuvanakirti Rasa*)	36.16±0.43	38.35±0.59	37.58±0.88	37.35±0.71	37.01±0.79	36.76±0.52
Group D (*Sudarshana Ghana Vati*)	36.38±0.35	38.98±0.41	38.45±1.00	37.95±0.85	37.62±0.78	37.22±0.79
Group E (*TribhuvanaMishrana*)	36.05±0.47	38.50±0.80	38.72±0.54	37.60±0.52	37.08±0.53	36.82±0.72
Group F (Standard group)	36.02±0.42	38.65±1.02	37.40±0.64	36.50±0.24	36.17±0.28	35.85±0.37
ANOVA	0.76	0.59	3.88	10.28	13.64	15.11
Significance	NS	NS	P<0.008	P<0.001	P<0.001	P<0.001
Significant pairs by post hoc test			control vs TKR controlvsstnd.	control vs TKR control vs TM controlvsstnd.	control vs TKR control vs SGV control vs TM controlvsstnd.	control vs GB control vs TKR control vs SGV control vs TM controlvsstnd.

Table 2 Paired t test of rectal temperature in albino rats at different hours between the groups

Test group	Paired t test between after yeast administration and 1 hr (p value)	Paired t test between after yeast administration and 2 hr (p value)	Paired t test between after yeast administration and 3 hr (p value)	Paired t test between after yeast administration and 4 hr (p value)
Group A (induced control)	0.50 (p<0.64)	0.47 (p<0.66)	0.81 (p<0.45)	0.52 (p<0.62)
Group B (*GodantiBhasma*)	1.00 (p<0.36)	0.78 (p<0.47)	1.34 (p<0.24)	2.46 **(p<0.05)**

Group C (*Tribhuvanakirti rasa*)	1.49 (p<0.19)	2.23 *(p=0.07)*	2.70 **(p<0.04)**	4.19 **(p<0.009)**
Group D (*Sudarshana Ghana Vati*)	1.83 (p=0.12)	4.40 **(p<0.007)**	6.34 **(p<0.001)**	6.89 **(p<0.01)**
Group E (*TribhuvanaMishrana*)	0.64 (p<0.55)	2.40 (p<0.06)	3.37 **(p<0.02)**	3.17 **(p<0.02)**
Group F (Standard group)	2.83 **(p<0.04)**	4.82 **(p<0.005)**	6.92 **(p<0.001)**	5.78 **(p<0.002)**

DISCUSSION

The Antipyretic study was screened by using yeast (Brewer's Yeast Aarkios Health Pvt. Ltd. Mumbai, India) induced hyper-pyrexia. Total 36 Albino Rats (6 groups) were selected and distributed six in each group and maintained at constant temperature of 25±0.5^{0}C for 24 hrs before experimental study. Initial rectal temperature of all rats was recorded individually before inducing pyrexia.

Pyrexia was induced by subcutaneous injection of 10 ml/kg of 20% Brewer's yeast solution, suspended in distilled water. After 18hrs of yeast injection rectal temperature was recorded using Digital Tele thermometer. Rise in temperature was observed from 36.25±0.274 to 38.30±1.1153 in group A, 36.033±0.4676 to 38.583±0.4792 in group B, 36.167±0.4272 to 38.350±0.589 in group C, 36.383±0.3488 to 38.983±0.4119 in group D, 36.050±0.4722 to 38.500±0.8075 in group E and 36.017±0.421 to 38.650±1.0252 in group F.

After 18hrs of yeast administration, drugs were administered orally to each group. In animals of Group-A (induced control) were administered with 5ml/kg distilled water orally. In animals of Group-B were administered with *Godanti Bhasma* in 90mg/kg, In animals of Group-C were administered with *Tribhuvanakirti Rasa* in 90mg/kg, In animals of Group-D were administered with *Sudarshana Ghana Vati* in 90mg/kg In animals of Group-E were administered with *Tribhuvan-Mishrana*in 90mg/kg oral. In animals of Group-F (standard group) were administered with standard drug Paracetamol 50 mg/kg.

After Ist hr. there was no statistical reduction in temperature seen in Group A, B,C, D and E but Group Fshowed significant reduction in temperature from 38.65±1.02 to 37.40±0.63 (<.04). So we can say that no one group of trial drug was show significant reduction in temperature.

After IIndhr. there was no statistical reduction in temperature seen in Group A, B and C but Group D there was statistical reduction from 38.98±0.41 to 37.95±0.85 (<.01). This indicated that *Sudarshan Ghana Vati* showed significant reduction in temperature at 2 hrs.

After III[rd] hr there was no statistical reduction in temperature seen in Group B. Group C showed significant temperature reduction from 38.35±0.58 to 37.02±0.80 (<.05). Group D showed statistical reduction in temperature from 38.98±0.41 to 37.62±0.78 (<.001). Group E also showed significant changes in temperature from 38.50±0.80 to 37.08±0.51 (<.05).*Sudarshana Ghana Vati*showed highly significant antipyretic activity at III[rd]hr. which was comparable to Paracetamol.

After IV[th]hr. there was statistical reduction in temperature seen in Group B, as the reduction in temperature from 38.58±0.47 to 37.73±0.52 ((<.05). In Group C reduction was found 38.35±0.58 to 36.77±0.52 (<.01). In Group D there was reduction in temperature from 38.48±0.411 to 37.21±0.79 (<.001).In Group E reduction in temperature was from 38.50±0.80 to 36.82±0.72(<.05).These reductions in temperature showed significant antipyretic activity of *GodantiBhasma*, *Tribhuvana-Mishrana, Tribhuvanakirti Rasa*and highly significant activity of *Sudarshana Ghana Vati* at IV[th]hr.

The above results showed that group D, group C, group E, group B of test samples and standard drug paracetamol highly significant antipyretic activity. Our formulation *Tribhuvana-Mishrana* showed significant results at III[rd] and IV[th] hr. *Sudarshana Ghana Vati*s howed significant reduction in elevated body temperature at 90mg/kg oral dose which is somewhat equal to paracetamol50mg/kg. The reason behind it is that the contents of *Sudarshana Ghana Vati* traditionally used as antipyretic and antiviral activity. Its chief ingredients *swertiachirayta* ethno medicinal herb, is known mostly for its bitter taste caused by the presence of different bioactive compounds such as amarogentin (most bitter compound till date), swerichian etc. it was proved that these compound have good antipyretic, antibacterial and antiviral activities[8,9]. the whole plant of *swertiachirayta* has been used for the treatment of antibacterial and anti fungal infections. Swerichian is known to be antipyretic and sweroside is reported to be antibacterial [10]. Other ingredients of *Sudarshan Ghana Vati* such as *urariapicta, curcuma longa, acoruscalamus, cyprusrotundus, zingiberofficinale, piper longum, azardiracthaindica, curcuma zedoaria, terminaliabellirica, picrorrhizakurroa, tinosporacordifolia, moringaoleifera, asparagus racemosus, berberisaristata , prunuscerasoides , pinuslongifolia, cinnamomumzeylanicum,cinnamomumtamala, desmodiumgangeticum, aconitum heterophyllum, aeglemarmelos,*

holarrhenaantidysentrica, glycerrhizaglabra, possess antipyretic and antimicrobial activity.

*Tribhuvanakirti Rasa*also showed good antipyretic activity may be due to the presence of *vatsanabha* and *trikatu* (*pippali, shunthi, maricha). Vatsanabha* have *swedajanana* property due to the presence of alkaloids. The active principles of *Trikatuchurna* like piperin, gingerol and inoleresin and other active constituents of *piper nigrum, piper longum* and *Zingiber officinale* might directly upon the CNS and decreases elevated body temperature[11].

The leaf extract of *nirgundi*have shown inhibitory effect on pseudomonas and solenacearum and Xanthomonas exenopodis. Thus it prove its antibacterial activity[12].

CONCLUSION

The results of present study are coherent with the Ayurvedicliterature in the drug efficacy study the dose of *Tribhuvana-Mishrana* and its ingredients showed anti pyreticeffect at various levels of significance.This drug is clinically can be used as antipyretic by ayurvedic physicians without showing any adverse effects for short period of time. Hence, *Tribhuvana-Mishrana*can be used at recommended dose and duration.

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