Journal of Pharmaceutical Research International

33(46A): 289-300, 2021; Article no.JPRI.73771
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparative Evaluation of Antipyretic Activity of an Ayurvedic Herbo-mineral Formulation *Dhatryadi Churna* and Its Modified Dosage form in Albino Wistar Rats

Bharat Rathi[1*], Sanket Shelke[2], Renu Rathi[3] and Devyani Awari[4]

[1]Department of Rasashastra and Bhaishajya Kalpana, Mahatma Gandhi Ayurved College Hospital & Research Center, Salod(H), Wardha, Maharashtra, India.
[2]Department of Rasashastra and Bhaishajya Kalpana Department, Mahatma Gandhi Ayurved College Hospital & Research Center, Salod(H), Wardha, Maharashtra, India.
[3]Department of Kaumarbhritya, Mahatma Gandhi Ayurved College Hospital & Research Center, Salod(H), Wardha, Maharashtra, India.
[4]Datta Meghe College of Pharmacy, DMIMS (DU) Salod (H), Wardha, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i46A32868
Editor(s):
(1) Dr. Takashi Ikeno, National Center of Neurology and Psychiatry, Japan.
Reviewers:
(1) Shruti R. Tarapure, India.
(2) K. Keerthana, Bharathidasan University, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73771

Original Research Article

Received 16 July 2021
Accepted 22 September 2021
Published 14 October 2021

ABSTRACT

Introduction: Experimental studies are essential and expected part of a new drug development. The studies are conducted to know about the toxic effects (if any), produced by the drug & to access safety of the drug. Studies also help to ascertain the efficacy of the drug & measures to be taken so as to curtail the toxic effects.
Aim & Objective: Study was aimed to do comparative evaluation of antipyretic activity of an Ayurvedic herbo-mineral formulation *Dhatryadi Churna* and its modified dosage form in experimental albino rats.
Materials and Methods: Present study was carried out at Animal house attached with the Institute.

**Corresponding author: E-mail: bharatrathi174@gmail.com;*

24 healthy Albino wistar rats of either sex weighing 180-200 gm were randomly selected and divided into 4 groups. Pyrexia was induced in rat by subcutaneous injection of 10 mL/kg b.w. of a 20% aqueous suspension of brewer's yeast. The trial drug *Dhatryadi Churna* and *Dhatryadi Vati* administered orally in the form of suspension to the albino rats.

Observation and Results: The present result shows that the *Dhatryadi Churna* (DC) and *Dhatryadi Vati* (DV) have a significant antipyretic effect in yeast induced pyrexia in rats. Hematological parameters were found to be within the normal biological and laboratory limits on comparison with the values of the control group.

Conclusion: *Dhatryadi churna* and *Dhatryadi Vati* does not show significant adverse effects on the blood, blood cells, and target organs at the doses used and can be safely used in human being.

Keywords: Dhatryadi churna; Dhatryadi vati; herbomineral formulation; antipyretic activity.

1. INTRODUCTION

In olden days all the leading authorities of Ayurveda have stressed the importance of four main *Pramanas* (modes of examining and acquiring the knowledge) to obtain the real knowledge of any *Padartha* (subject of knowledge). In other words, these four Pramanas served as different evidences or different methods to prove truthfulness of a matter. They are *Prathyaksha* (direct evidence), *Anumana* (Inference), *Yukti* (rational) and *Aptopadesha* (authoritative person) [1-2]. The present era is of sciences. Scientific fraternity believes only in proved facts or they require rationality behind facts. The entire suggestion has to be proved by the available, affordable parameters or experiments to establish the facts. Then only that will be accepted by the modern people. Ayurveda has also accepted the importance of visible facts by saying that so it is essential to prove all the Ayurveda theories and drug efficacy scientifically. In the process of new drug development, experimental study is the first step to know the efficacy and safety of the drug. Experimental studies are essential and expected part of a new drug development. The studies are conducted to know about the toxic effects (if any), produced by the drug & to access safety of the drug. Studies also help to ascertain the efficacy of the drug & measures to be taken so as to curtail the toxic effects [3].According to ethics it has been stated that before application of the new drug to the society it should be tested on animals having similar behavior pattern and physiological function as that of humans. Pharmacological studies, conducted on experimental models helps in ascertaining the mode of action of drug, along with its pharmaco-kinetic and pharmaco-dynamic properties [4]. So it is essential to prove all the Ayurvedic principles and drug efficacy scientifically by modern parameters, through which Ayurveda can excel in current era as "Evidence based, well documented system of medicine. The study was aimed to do comparative evaluation of antipyretic activity of an Ayurvedic herbo-mineral formulation *Dhatryadi Churna* and its modified dosage form in experimental albino rats. Herbal powder is one of the most often used traditional dose forms in Ayurvedic medicine, and it is used to treat a variety of ailments. *Churna* is the fine powder of a completely dry medication sifted through a clean cloth in general [5].

2. MATERIALS AND METHODS

Collection of the raw drugs: All the ingredients were procured from the Ayurveda pharmacy of the institute. All the raw drugs were authenticated from Department of Dravyaguna of the same institute. The formulation selected for the present study *Dhatryadi churna* was prepared in the P.G Lab of Rasa Shastra and Bhaishajya Kalpana department under expert supervision. Its modified form *Dhatryadi vati* was prepared by giving the three *bhavana* of decoction of the same ingredients to the *Dhatryadi churna* and then punched through tableting machine. Each tablet weighed 250 mg [6].

Materials: Digital Clinical thermometer: Obtained from animal house. Thermometer has thermo-sensitive and digital display screen to display temperature in Fahrenheit scale which beeps on recording accurate temperature. Glycerine applied thermo sensitive tip is inserted into the rectum of the rat and should be kept for one minute for obtaining the accurate temperature. Brewer's yeast [Baker's yeast] - 500g of dried Brewer's yeast was purchased online from Amazon. Calpol [Paracetamol] suspension (5ml containing 120 mg of Paracetamol) - Manufactured by Dr. Reddy Pharmaceuticals Limited was purchased from local medical store as standard drug.

Selection of animals: 24 healthy Albino wistar rats of either sex weighing 180-200 gm were randomly selected and grouped into four (Group I to Group IV), so that each group consisted of 6 rats. They were marked with sketch pens for their individual identification.

Rat Maintenance: Animals were well maintained under identical condition of place, light, temperature, humidity, food and other conditions at the animal house. Before the commencement of the experiment all 8 cages required for the experiment were cleaned once in 3 days and there after regularly till the end of experiment. Cages were washed with detergent followed by disinfectant phenol solution to maintain the hygiene. Bedding material was prepared using paddy husk, which was changed once in three days till the end of experiment.

Feeding Schedule: The quantity of food for rats weighing180-200 gm was about 18-20 gm / day. Readymade rat feed prepared by Lipton India Ltd was procured & used. Water was provided as required with the feeding bottles.

3. METHODOLOGY

Brewer's Yeast Induced Pyrexia Method: Pyrexia was induced in rat by subcutaneous injection of 10 mL/kg b.w. of a 20% aqueous suspension of brewer's yeast in the back below the nape of the rat [7-8]. It induces pyrexia in 1 hr. The trial drug *Dhatryadi Churna* and *Dhatryadi Vati* administered orally in the form of suspension to the albino rats in calculated dose as shown in the Table 2.

Procedure: Animals were kept on fasting overnight, but were provided with drinking water. Next morning, the initial rectal temperatures of all rats were recorded. After two hours of induction of fever, the respective DC and DV group drugs were administered through stainless steel oral feeding needles. Calculated quantity of drug was taken in the syringe and pushed directly in a single dose. Rectal temperatures recorded at a regular interval of 1 hr for 14 hours.

Hematological Findings: Twenty-four hours after the last dose, blood samples were collected for estimation of hematological parameters CBC-Hb%, RBC count, Platelet count, MCH, MCHC, MCV and HCT were assessed using an automated machine (Automated CBC Analyzer: Sysmex KX-21).

3. OBSERVATION AND RESULTS

Evaluation: The difference between actual values and initial values were registered for each time interval. The maximum reduction in rectal temperature in comparison to the standard positive was calculated and results were compared with the effect of standard drug, Paracetamol.

Table 1. Grouping and posology

Sr no.	Grouping	No. of rats	Drug administered	Dose/200g,body wt
01	**Negative Control (NC)**	6	Gum Acacia	2 ml
02	**Standard Control (SC)**	6	Paracetamol suspension	1.6 ml
03	***Dhatryadi Churna* (DC)**	6	*Dhatryadi Churna*	0.216 mg
04	***Dhatryadi Vati* (DV)**	6	*Dhatryadi Vati*	9 mg

Table 2. Behavioral observations in animals

Sr no.	Observations	Before the induction of Pyrexia (-14 hours)	14 hours after induction of Pyrexia (+ 14 hours)
01	Temperature	Normal body temperature	Raised body temperature above normal when felt with touch
02	Activities	More active	Decreased activities
03	Behavior[8]	Normal with good food and water intake	Dull looking Face bent downwards Looking tired & Scanty maturation Less food and water intake Trying to sleep one over the other

Table 3. Comparison of normal body temperature in four groups

Groups	N	Mean (^{0}C)	Std. Deviation	Std. Error	Minimum	Maximum
NC	6	94.15	0.56	0.23	93.60	95.10
SC	6	94.53	0.75	0.30	93.70	95.60
DC	6	94.15	0.56	0.23	93.60	95.10
DV	6	94.53	0.75	0.30	93.70	95.60

Table 4. Comparison of grant average temperature in four groups

Groups	N	Mean (^{0}C)	Std. Deviation	Std. Error	Minimum	Maximum
NC	6	95.48	0.30	0.12	94.98	95.89
SC	6	100.87	0.31	0.13	100.67	101.51
DC	6	100.87	0.31	0.13	100.67	101.51
DV	6	100.87	0.31	0.13	100.67	101.51

4. DISCUSSION

Pyrexia inducing action of yeast Brewer's yeast is a fungi containing lipo-polysaccharide, which is a cell wall component of gram negative bacteria [9]. It binds with macrophages, releasing cytokines, interleukin - 1 etc into the blood circulation, leading to antigen-antibody reaction. Then it reduces blood brain barrier and releases Arachidonic acid mediated by the enzymes phospholipase, prostaglandin E2 synthase, and cyclooxygenase [10]. Finally synthesis and release of PGE2 into anterior hypothalamus result in pyrexia [11-12]. Experimental evaluation of antipyretic effect has been carried out in albino wistar rats. Trial drugs were subjected to evaluation in a set of standard experimental albino rats. They were divided into 4 groups as NC group, SC group, DC group and DV group consisting of six rats in each group [13]. 20% yeast solution was prepared in normal saline and given orally with 1ml / 100gm body weight dose. Group NC was treated with distilled water to serve as Control. Group SC was treated with Standard drug, i.e. Paracetamol (PCM) suspension 1.6 ml/ 200 gm BW. Group DC was treated with *Dhatryadi Churna* (DC*)*. Group DV was treated with *Dhatryadi Vati* (DV) at a dose of 0.216 mg and 9 mg/200 gm BW of rat respectively. Rat dose has been fixed by using a standard rat dose conversion formula. After administration of respective trial groups, hourly temperature was recorded for 14 hours. By observing the readings, marked relief was observed in trial and standard drugs when compared with the Control. This suggests the positive effect of all the trial drugs in controlling pyrexia.

The results of statistical test performed, the mean of all the four groups differ significantly, which is mainly due to non-administration of any medication to control group where as in standard group and both the trial groups the medication helped to reduce the temperature at the faster rate. To know the level of significance again students paired't' test has been carried out. The mean of temperature in rats of NC group was 94.15 ± 0.56, in group SC it was 94.53 ± 0.75, in group DC it was 94.15 ± 0.56 and group DV it was 94.53 ± 0.56 by using one way ANOVA statistical no significant variation was found in normal body temperature of rat in all 4 groups [F= 0.65, p=0.58] on comparing normal body temperature of rat in four groups statistical significant difference found in all 4 groups. [p< 0.05]. (Table 3) The mean of rat in NC group was 95.48 ± 0.30, in group SC it was 100.87 ± 0.31, in group DC it was 100.87 ± 0.31 and group DV it was 100.87 ± 0.31 by using one way ANOVA statistical test no significant variation was found in grant average temperature of rat all 4 groups [F= 437.58, p=0.0001] on comparing grant average temperature of rat in four groups statistical significant difference found in all 4 groups. [p< 0.05]. (Table 4) On comparing the above results it has been found that both the trial groups and standard group are more effective than control group due to the administration of the medication. The mean of rat in NC group was 9.60 ± 1.02, in group SC it was 6.57 ± 1.64, in group DC it was 7.59 ± 1.12 and group DV it was 7.21 ± 1.13.

By using one way ANOVA statistical test no significant variation was found in RBC count of rat in all 3 groups [F= 6.50, p=0.003] on comparing RBC count of rat in normal group statistical significant difference found in all 3 groups. [p is more than 0.05]. (Graph 5)

The mean of rat in NC group was 18.13 ± 2.10, in group SC it was 14.30 ± 1.25, in group DC it was 15.23 ± 0.87 and group DV it was 14.23 ±

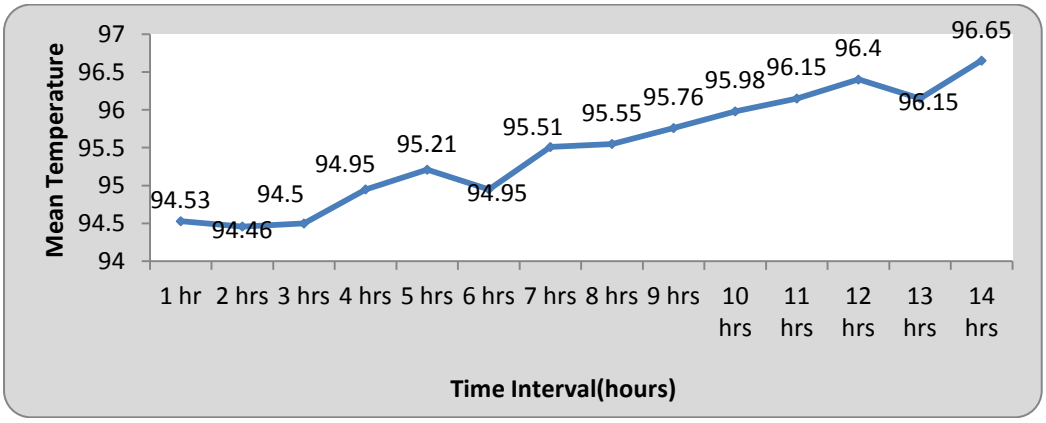
2.61 by using one way ANOVA statistical no significant variation was found in Hb% of rat all 3 groups [F= 5.92, p=0.005] on comparing Hb% of rat in normal groups statistical significant difference found in all 4 groups. [p is more than 0.05]. (Graph 6).

The mean of rat in NC group was 456.16 ± 70.83, in group SC it was 566.83 ± 127.23, in group DC it was 501.33 ± 100.05 and group DV it was 568.83 ± 132.41 by using one way ANOVA statistical non significant increase in platelet were observed in all 3 groups (standard, DC and DV) [F= 1.47, p=0.25] on comparing platelet of rat in normal control groups statistical significant difference found in all groups. [p is more than 0.05]. (Graph 7).

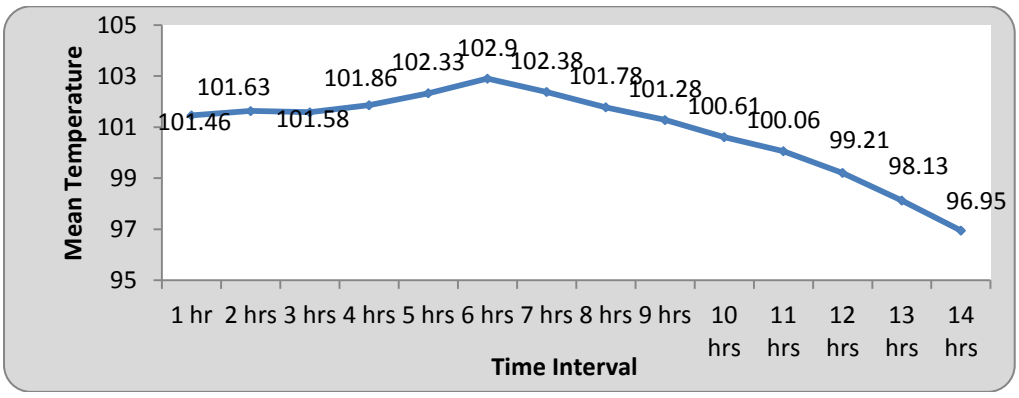
The mean of rat in NC group was 18.88 ± 0.79, in group SC it was 19.60 ± 0.97, in group DC it was 20.35 ± 2.44 and group DV it was 19.70 ± 1.98 by using one way ANOVA statistical no significant variation was found in MCH count of rat all 3 groups [F= 0.75, p=0.53] on comparing MCH count of rat with normal control groups statistical significant difference found in all groups [p is more than 0.05]. (Graph 8).

The mean of rat in NC group was 34.75 ± 0.68, in group SC it was 39.51 ± 7.75, in group DC it was 37.56 ± 3.53 and group DV it was 39.50 ± 5.35 by using one way ANOVA statistical no significant variation was found in MCHC count of rat all 3 groups [F= 1.16, p=0.33] on comparing MCHC count of rat in normal control groups, statistical significant difference found in all groups [p is more than 0.05]. (Graph 9).

The mean of rat in NC group was 54.33 ± 2.06, in group SC it was 53.66 ± 2.50, in group DC it was54.16 ± 1.83 and group DV it was 50.00 ± 2.36 by using one way ANOVA statistical no significant variation was found in MCV of rat all 3 groups [F= 5.16, p=0.008] on comparing MCV of rat in normal control groups, statistical significant difference found in all groups [p is more than 0.05]. (Graph 10).

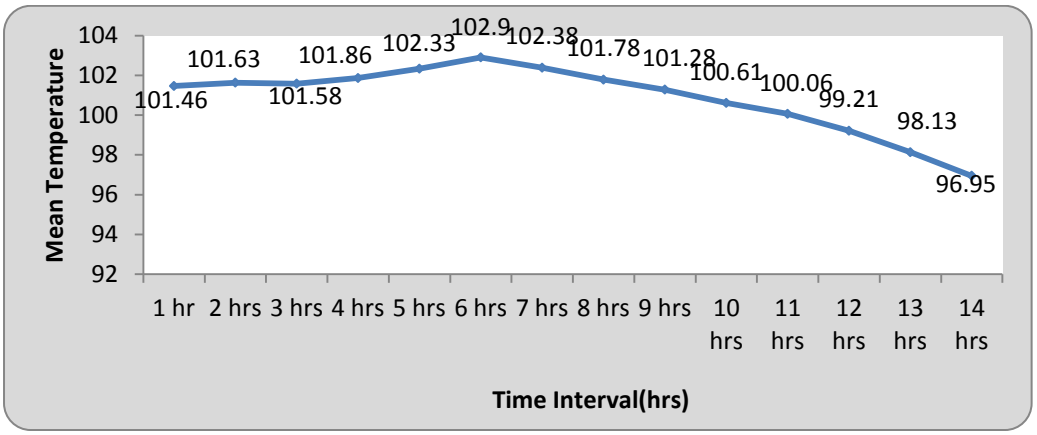


Graph 1. Comparison of temperature in NC group at various time interval

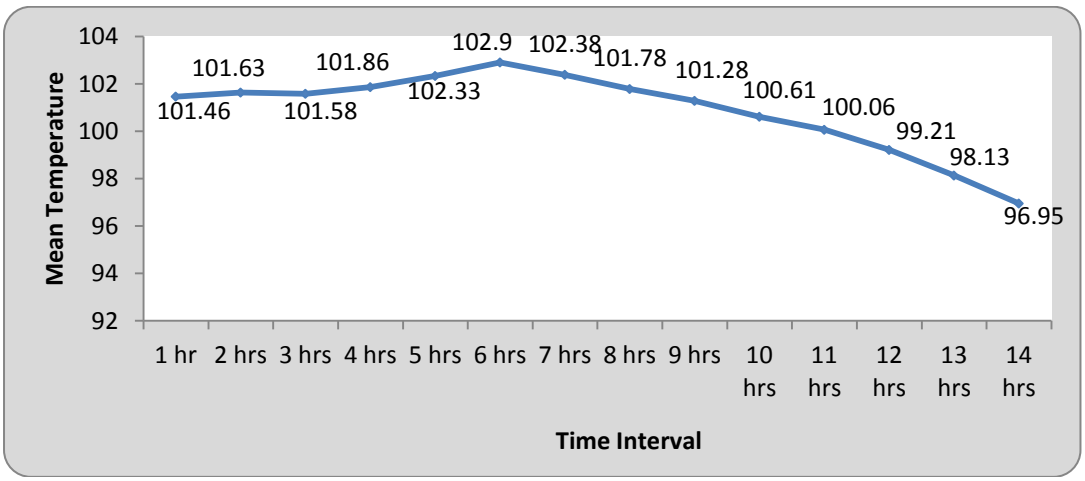


Graph 2. Comparison of temperature in SC group at various time interval

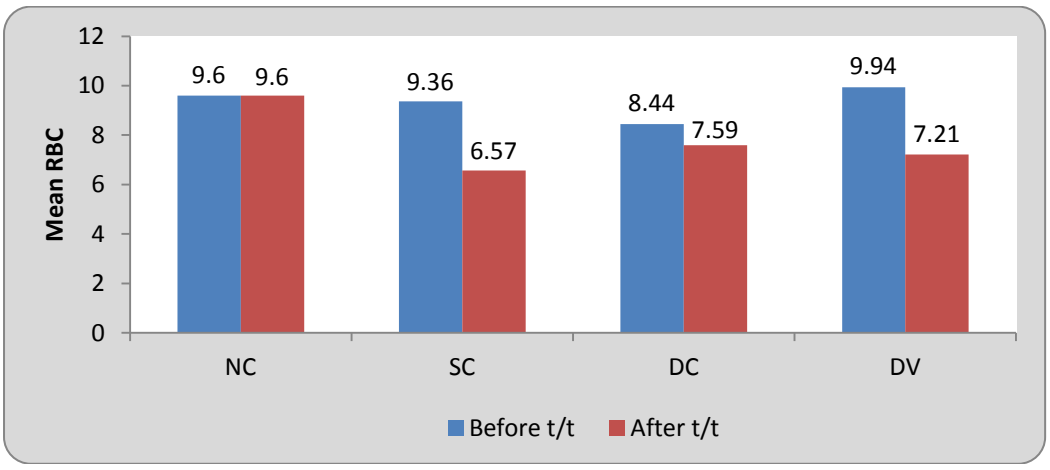
The mean of rat in NC group was 52.23 ± 6.56, in group SC it was 36.85 ± 5.15, in group DC it was 40.95 ± 5.38 and group DV it was 36.21 ± 6.27 by using one way ANOVA statistical no significant variation was found in HCT count of rat all 4 groups [F= 9.56, p=0.0001] on comparing HCT count of rat in normal control groups, statistical significant difference found in all groups [p is more than 0.05]. (Graph 11)



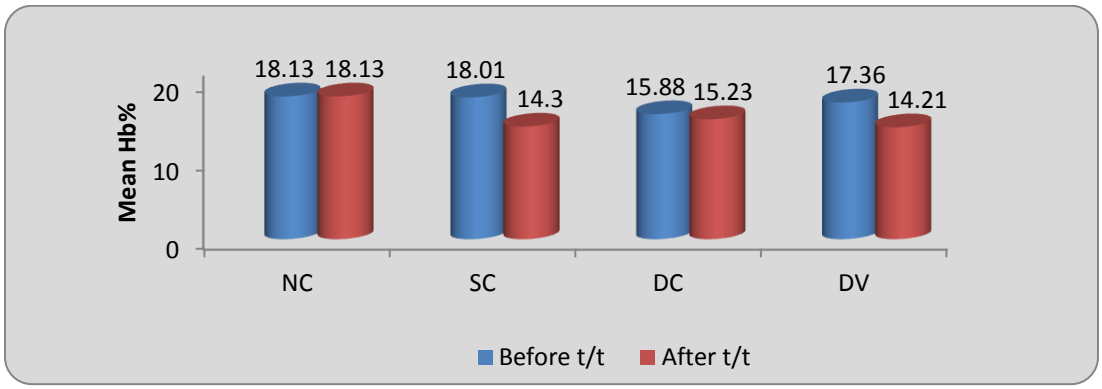
Graph 3. Comparison of temperature in DC group at various time interval



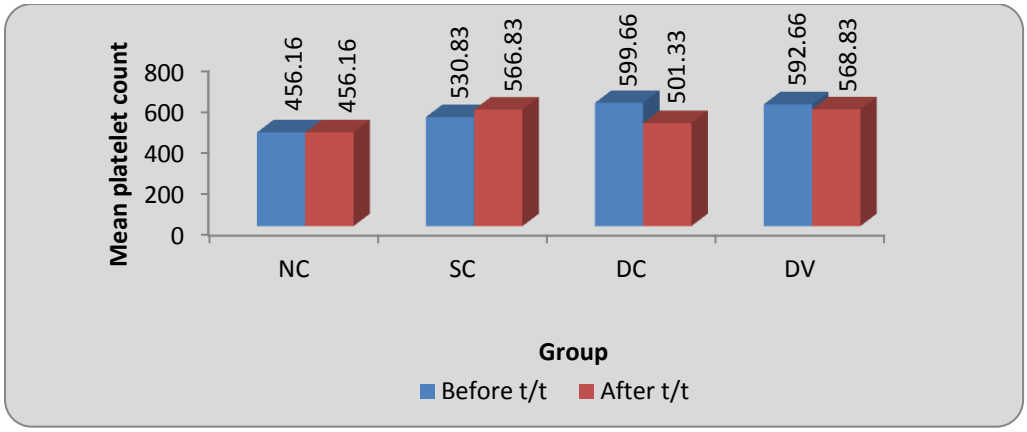
Graph 4. Comparison of temperature in DV group at various time interval



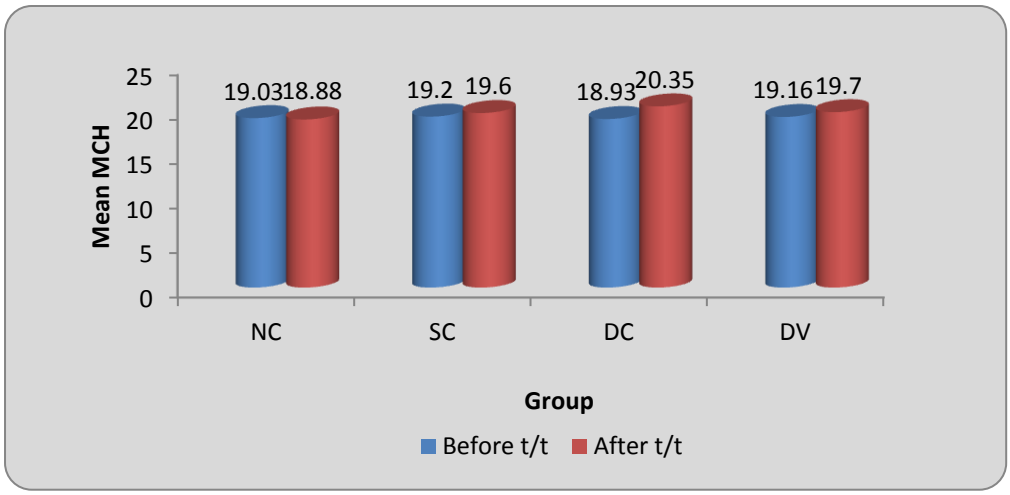
Graph 5. Comparison of RBC in four groups before and after t/t



Graph 6. Comparison of Hb% in four groups before and after t/t



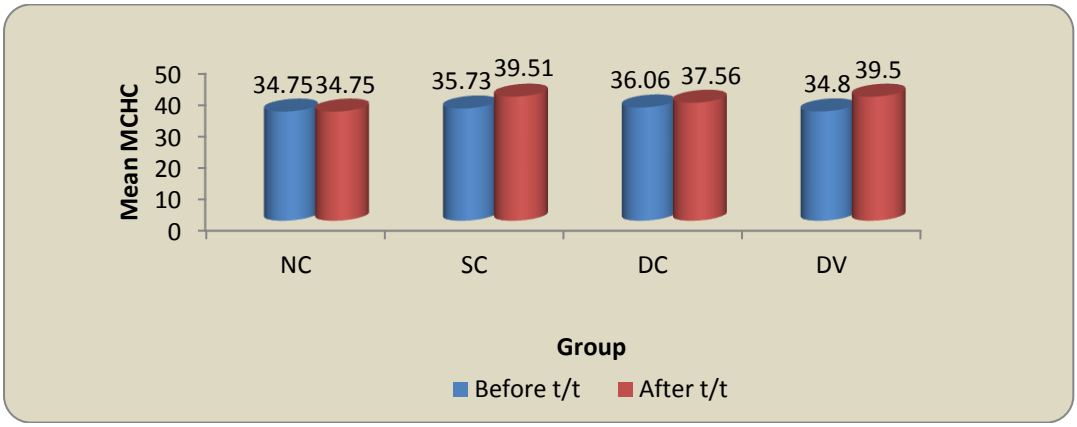
Graph 7. Comparison of PLT in four groups before and after t/t



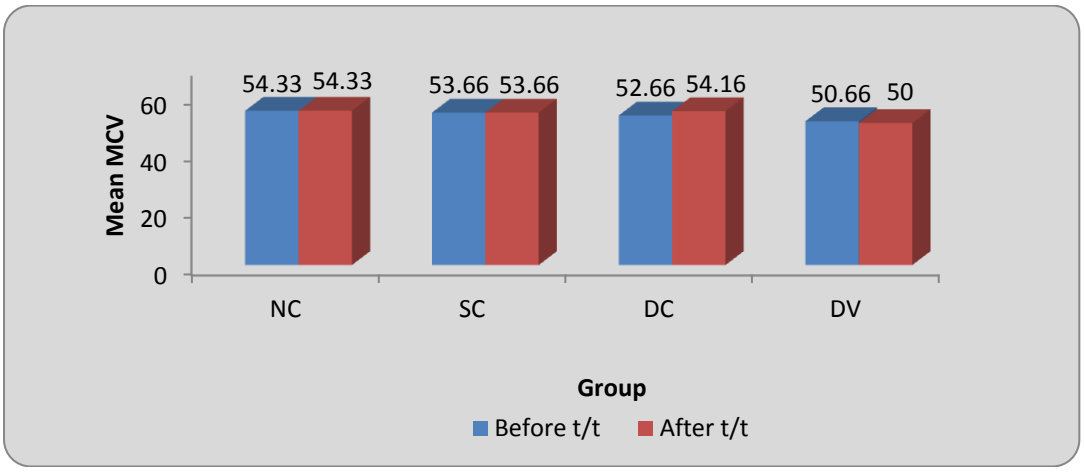
Graph 8. Comparison of MCH in four groups before and after t/t

On comparing the standard group with both the trial groups, the standard group even though is having similar anti-pyretic action but still on comparing the individual means it is bit effective than trial groups. On comparing both the trial drugs with each other even though they are having similar anti pyretic action on comparing the individual means i.e. DV is more effective than DC. Pyrexia may be as result of infection or one of the sequel of tissue damage, inflammation, graft rejection or other disease state. Antipyretics are drugs which reduce

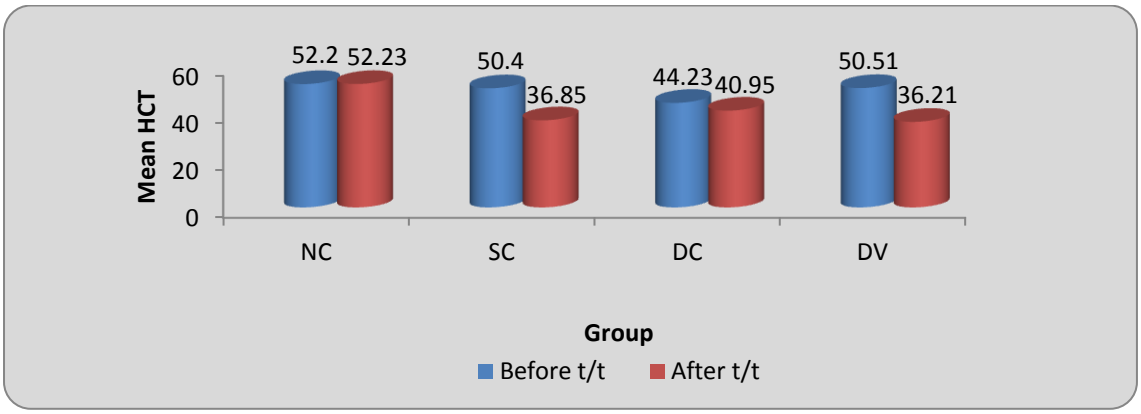
elevated body temperature, graft rejection or other disease state. Regulation of body temperature requires a delicate balance between production and loss of heat and the hypothalamus regulates the set point at which body temperature is maintained. Most of the antipyretic drugs inhibit COX-2 expression thus inhibiting PGE2 biosynthesis to reduce elevated body temperature [10]. The present result shows that the *Dhatryadi Churna* (DC) and *Dhatryadi Vati* (DV) have a significant antipyretic effect in yeast induced pyrexia in rats.



Graph 9. Comparison of MCHC in four groups before and after t/t



Graph 10. Comparison of MCV in four groups before and after t/t



Graph 11. Comparison of HCT in four groups before and after t/t

There is an extensive evidence to implicate free radicals in the development of disease. Free radicals have been implicated in the causation of ailments such as fever, diabetes, liver cirrhosis etc [14]. The antioxidant activity of Ascorbic acid, Riboflavin, Tannin, Ellagic acid, Lupeol, Tannic acid, Sesamin and plumbagin may helpful in either inhibiting or scavenging radicals. Reactive oxygen damages an important cellular components causing tissue injury through covalent binding and lipid per oxidation. In a previous study, the increase in the body temperature intensified the lipid peroxidation process, which indicates that pyrexia is associated with increased oxidative stress [15]. The antioxidant supplementation decreased the lipid peroxidation process. The flavonoids reported to have antioxidant activity. Hence, antioxidant activity may be one of the possible mechanisms by which it reduces the elevated body temperature. Yeast-induced pyrexia is called pathogenic fever and its etiology involves production of prostaglandins.

Most of the marketed preparations, drug compounds and toxic substances which are foreign to our body target the blood system ie. hematopoietic system, an important index of bodies physiology involved in the creation of the cells of blood and determining the pathological status in rodent and human being [16]. Hematological analysis shows the picture of the values of the different parameters examined like complete blood count (CBC), hemoglobin Hb%, Red blood cell (RBC) count, Platelet count, mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), Mean corpuscular volume (MCV) and HCT were found to be within the normal biological and laboratory limits on comparision with the values of the control group. No significant changes were observed in all the treated groups as compared to the normal control groups. This indicates that the *Dhatryadi churna* and *Dhatryadi Vati* does not show significant adverse effects on the blood, blood cells, and target organs at the doses used. In the present study, from result it is cleared that, both the herbo mineral formulations DC and DV also significantly increases the platelet count as compare to normal control thus played an important role in increasing immunity and due to presence of many active substances like flavonoids may be involve in balancing the redox parameter thus protect from oxidative stress.

Dhatryadi Churna (DC) and *Dhatryadi Vati* (DV) showed significant antipyretic activity and the effects are comparable to standard drug Paracetamol (PCM) that may be due to inhibition of prostaglandin synthesis. Again, many researchers reported that the formulations containing alkaloids, tannins, carbohydrates and flavonoids have been reported antipyretic potential in various studies. In many earlier studies flavonoids compounds have been reported to exhibit antipyretic effect, as some flavonoids are predominant inhibitors of cyclo oxygenase or lipo oxygenase [17]. So *Dhatryadi Vati* (DV) form is therapeutically more effective than *Dhatryadi Churna* (DC). Paracetamol is an analgesic but is also an effective febrifuge. It is a poor inhibitor of cyclo oxygenase in the presence of peroxides that are found in inflammatory lesions. In contrast, its antipyretic effect may be explained by its ability to inhibit cyclo oxygenase in the brain, where peroxide tone is low. Further, it does not inhibit neutrophil activation. In supra-pharmacologic doses it inhibits NF-kB stimulation of inducible nitric oxide synthase [18]. In the present study, in the standard control group the rise in temperature was consistent and significant in comparison to the initial values. In the Negative control group also the rise in temperature was significant; however, the magnitude was slightly less in comparison to that in the standard control group in the initial stages. Both the *Dhatryadi Churna* and *Dhatryadi Vati* samples produced very good antipyretic effect in a dose-dependent manner and the observed effect were almost similar to that in the paracetamol- treated group. *Churna Kalpana* being the most commonly preferred dosage form holds certain disadvantages like higher chances of oxidation and hydrolysis, non-palatability, low shelf life to overcome these issues DC modified into DV, holding the advantages as higher shelf life, easy for administration and fixed dosage.

5. CONCLUSION

The comparison of Anti Pyretic activity in experimental study clearly indicates that DV possess significantly higher efficacy than DC and PCM (p value – 0.005). Thus, *Dhatryadi Churna* can be replaced by modified dosage from *Dhatryadi Vati* and the present formulation should be studied in clinical study in human trials to assess the antipyretic action as it may be a replaced by standard paracetamol of alternate natural safe formulation.

IMAGES OF EXPERIMENTAL STUDY

Plate 1. Preparation of animal

Plate 2. Marking in Rats

Plate 3. Pyrexia Inducing

Plate 4. Measuring temperature after inducing pyrexia

Plate 5. Standard Drug Given (PCM)

Plate 6. Dhatryadi Churna Given

Plate 7. Dhatryadi Vati Given

Plate 8. Measuring temperature after given Medication

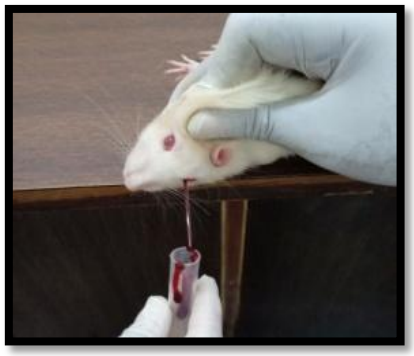


Plate 9. Blood Sampling

RESEARCH SIGNIFICANCE

The study highlights the efficacy of " an Ayurvedic formulation " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Present study was carried out at Animal house attached with the Institute. After approval from institutional animal ethics committee (Ref. no. DMIMS (DU)/IAEC/2018- 19/08 on dated 14th Aug 2018 the study was commenced as per plan.

ACKNOWLEDGEMENT

Author would like to thank DMIMSU for motivating and providing all necessary help for writing this article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Acharya Agnivesha, Charaka Samhita, Chikitsasthana Jwarachikitsa/31; revised by Charaka & Dradhabala, with Ayurveda Dipika commentary of Chakrapanidatta, edited by Vaidya Yadavji Trikamji Acharya, Chaukhambha orientalia, Varanasi, reprint. 2009;117.
2. Shastri Shrilaxmipati, Yogaratnakar, reprint Varanasi, Chaukhambha Sanskrit Sansthana. 2005;230.
3. Peck CC, Barr WH, Benet LZ, Collins J, Desjardins RE, Furst DE, Harter JG, Levy G, Ludden T, Rodman JH, Sanathanan L. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. Journal of pharmaceutical sciences. 1992;81(6):605-10.
4. Esch MB, King TL, Shuler ML. The role of body-on-a-chip devices in drug and toxicity studies. Annual review of biomedical engineering. 2011;13:55-72.
5. Shelke S, Rathi B. Review on *Dhatryadi Churna*: An Ayurvedic Antipyretic Polyherbal Formulation. Indian Journal of Forensic Medicine & Toxicology, October-December 2020;14(4):6968-6972.
6. Shelke SB, Rathi B, Wanjari A, Rajput D. Pharmaceutico-analytical standardization and drug dosage modification of *Dhatryadi Churna*. J Indian Sys Medicine 2020;8: 200-9.
7. Nisar M, Khan I, Simjee SU, Gilani AH, Perveen OH. Anticonvulsant, analgesic and antipyretic activities of *Taxus wallichiana* Zucc. JEthnopharmacol. 2008; 116:490–494.
8. Aiyalu R, Ramasamy A, Shanmugasundaram M. Evaluation of antipyretic activity of ethyl acetate extract of *Adenema hyssopifolium* G. Don in a rat model. Asian Paci J Trop Med. 2010;3:523–526.
9. Satoshkar RS, Bhandarkar SD, Ainapure SS. Pharmacology and Pharmaco-therapeutics, popular Prakashan, Mumbai, 16th edition. 1999;153.
10. Timbadiya MJ, Nishteswar K, Acharya R, Nariya MB. Experimental evaluation of antipyretic and analgesic activities of Amalakyadi Gana: An Ayurvedic formulation. Ayu. 2015;36(2):220.
11. Dalal S, Zhukovsky DS. Pathophysiology and management of fever. Journal of Supportive Oncology. 2006;4:9–16.
12. Li S, Ballou LR, Morham SG, Blatteis CM. Cyclooxygenase-2 mediates the febrile response of mice to interleukin-1β. Brain Research. 2001;910: 163–173.
13. Kalpana B. Dissertation Submitted To The (Doctoral Dissertation, Rajiv Gandhi University of Health Sciences). A Comparative Pharmaceutical & Experimental Study of Amalakyadi Kwatha and Ghanavati W. S.R. To Its Anti-Pyretic Action; 2014.
14. Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. Pharmacognosy reviews. 2010 ;4(7):27.
15. Singh RH. Exploring larger evidence-base for contemporary Ayurveda. International journal of Ayurveda Research. 2010;1 (2):65.
16. Mukinda JT, Syce JA, Acute and chronic toxicity of the aqueous extract of Artemisia afra in rodents, Journal of Ethnopharmacology. 207;112(1):138–144.

17. Harisson TR, Harisson"s Principles of internal medicine, McGraw-Hill medical publishing divison, 16th edition. 2005; 60.

18. Goodman and Gilman's, The Pharmacological Basis of Therapeutics. Joel GH, Lee EL. 10th ed. New York: McGraw-Hill Medical Publishing Division. 2001;703-04.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/73771