

RESEARCH ARTICLE

Evaluation and comparison of antipyretic activity of aqueous leaf extracts of *Vitex negundo* and *Andrographis paniculata* in rabbitsNaveen Pokala¹, Naveen Alasyam², Kavitha Rasamal¹¹Department of Pharmacology, Mamata Medical College, Khammam, Telangana, India, ²Department of Pharmacology, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India

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ABSTRACT

Background: *Vitex negundo* and *Andrographis paniculata* have a multitude of remedies for several diseases. As the treatment of fever was one such remedy, we found that not much work has been done on the antipyretic effect of these plants. **Aims and Objective:** The aims and objective of this study were to evaluate and compare the antipyretic activity of aqueous leaf extracts of *V. negundo* and *A. paniculata* in rabbits. **Materials and Methods:** Laboratory breed New Zealand strains of rabbits of either sex weighing 1000–1500 g were used in the study. The animals were divided into five groups ($n = 6$) in both the sets. The rabbits of all the groups were made febrile by administering misoprostol (prostaglandin E1) subcutaneously in the dose of 100 mcg/kg. For Groups 1 and 2, normal saline 2 ml/kg as control and aspirin 28 mg/kg as standard were given, respectively, in both the sets. *V. negundo* and *A. paniculata* in the doses of 200, 400, and 800 mg/kg were given in remaining three groups of both sets, respectively. Rectal temperatures were monitored for every 30 min after treatment started up to 240 min, and its effects were compared to aspirin. **Results:** Aqueous extracts of *V. negundo* and *A. paniculata* produced highly significant ($P < 0.001$) antipyretic effect in 400 and 800 mg/kg doses. However, the onset of action was fast with *V. negundo*. **Conclusion:** The study concludes that aqueous extract of *V. negundo* has fast onset and sustained antipyretic action in New Zealand rabbits, whereas *A. paniculata* has delayed onset and sustained antipyretic effect.

KEY WORDS: *Andrographis paniculata*; Antipyretic; Digital Thermometer; Prostaglandin E1; *Vitex negundo*

INTRODUCTION

Fever or pyrexia is may be due to infection, inflammation, tissue damage, graft rejection, and any disease states.^[1] Pyrexia is one of the most common medical signs. Antipyretics are the agents which reduce the elevated body temperature. They act centrally on the temperature regulation center in

the brain and also act peripherally through vasodilatation by promoting heat loss. Most of the antipyretic drugs act by inhibiting cyclooxygenase (COX)-2 expression, which inhibits prostaglandin PGE2 biosynthesis. As synthetic COX inhibitors are toxic to hepatic, brain cells, cortex, glomeruli, and heart muscles,^[2] natural antipyretic agents with less or no toxicity are essential. In spite of the newer advancements in synthetic drug development, plants are the major sources for raw materials in drug development. Herbal formulations are not known to cause any notable adverse effects^[3] and are readily available at cheaper prices.

Vitex negundo,^[4] a large aromatic shrub with purple flowers, has been used by Ayurveda, Unani, and Siddha for different disorders. Analgesic and anti-inflammatory actions of

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negundo seeds have been studied thoroughly.^[5,6] *Andrographis paniculata*^[7] is an herbaceous plant in the Acanthaceae family, commonly known as the king of bitters.^[8] Mature leaves of this plant are used for the treatment of fever, common cold, and infectious diseases.^[9-11]

While searching for plants used for treating fever, *V. negundo* and *A. paniculata* were attracted us because they had a multitude of remedies for several diseases. As the treatment of fever was one such remedy, we found that not much work has been done on the antipyretic effect of these plants. Antipyretic action of *V. negundo* was well studied using yeast-induced hyperpyrexia method.^[12] As PGE1-induced hyperpyrexia models are very few in the literature, we followed this method.

MATERIALS AND METHODS

This study was carried out in Mamata Medical College, Khammam, Telangana.

Animals

Laboratory-bred New Zealand strains of rabbits of either sex, weighing 1000–1500 g, procured from the animal house of Mamata Medical College were used for the study. The animals were maintained under standard laboratory conditions at 25°C, commercial pellet diet with water *ad libitum*, and normal photoperiod (12 h dark/12 h light). The experimental protocol has been approved by the Institutional Animal Ethics Committee.

Drugs and Chemicals

Aspirin was purchased from Bayer's Pharmaceuticals, U.S, and Misoprostol–Misoprost from Cipla Pharmaceuticals, India.

Instruments

Medical Digital Thermometer, Sanitas, India, was used.

Animal Dose Calculation from Human Dose^[13]

Aspirin (Human dose = 600 mg).

For Rabbit = $600 \times 0.07 = 42/1500$ g rabbit = 28 mg/kg

Plant Material and Extraction Procedure

The dried leaves of *V. negundo* and *A. paniculata* were collected from the local market and authenticated by Professor and Head, Department of Botany, Government Degree College, Khammam. The preparations of crude leaf extract of *V. negundo* and *A. paniculata* were done in the Department of Pharmacology, using continuous hot percolation process with Soxhlet apparatus.^[14]

Acute Toxicity Study and Establishment of Dose of the Extract^[15,16]

Acute toxicity tests in rabbits have proven the LD₅₀ of leaf extract of *V. negundo* 7.58 g/kg and LD₅₀ of leaf extract *A. paniculata* to be >4.7 g/kg. Based on the results obtained from this study, the doses of aqueous leaf extracts of *V. negundo* and *A. paniculata* for antipyretic activity were fixed to be 200, 400, and 800 mg/kg body weight.

Inclusion Criteria

The following criteria were included in the study:

- New Zealand strains of rabbits of either sex, weighing 1000–1500 g.
- Healthy with normal behavior and activity.
- Rabbits having normal rectal temperature at start of the experiment.

Exclusion Criteria

The following criteria were excluded from the study:

- New Zealand strains of rabbits weighing <1000 g or >1500 g.
- Pregnant and lactating animals.
- Animals with systemic and skin infections.

Experimental Design

Rabbits were used for the evaluation of the antipyretic effect of aqueous leaf extracts of *V. negundo* and *A. paniculata*. The animals were divided into five groups ($n = 6$) in both the sets.

SET-1 for *V. negundo*

Group number	Group name	Drugs and Dose
Group 1	Control	NS 2 ml/kg
Group 2	Standard	Aspirin 28 mg/kg
Group 3	Test 1	ALEVN 200 mg/kg
Group 4	Test 2	ALEVN 400 mg/kg
Group 5	Test 3	ALEVN 800 mg/kg

ALEVN: Aqueous leaf extract of *V. negundo*. *V. negundo*: *Vitex negundo*

SET-2 for *A. paniculata*

Group number	Group name	Drugs and Dose
Group 1	Control	NS 2 ml/kg
Group 2	Standard	Aspirin 28 mg/kg
Group 3	Test 1	ALEAP 200 mg/kg
Group 4	Test 2	ALEAP 400 mg/kg
Group 5	Test 3	ALEAP 800 mg/kg

ALEAP: Aqueous leaf extract of *A. paniculata*. *A. paniculata*: *Andrographis paniculata*

Before the experiment, rectal temperatures of the rabbits were recorded by inserting a well-lubricated bulb of a thermometer

into the rectum. Care was taken to insert it to the same depth each time (about 6 cm).^[17] The rabbits were made febrile by administering misoprostol (PGE1) subcutaneously in the dose of 100 mcg/kg and the temperatures were recorded.^[18] A control group was maintained by administering 2 ml/kg normal saline orally and the temperature was recorded. The standard drug aspirin was administered orally in the dose of 28 mg/kg and the temperature was recorded. Then, the test drugs, i.e., extracts of the plants were administered in different doses and the temperatures were recorded for every 30 min up to 240 min, and the observed results were tabulated and statistically analyzed.

Statistical Analysis

The statistical analysis of data was performed using one-way analysis of variance followed by Bonferroni post-test using the software GraphPad Prism, version 5.01. $P < 0.05$ was considered to be statistically significant.

RESULTS

The Effect of *V. negundo*

The different doses of aqueous leaf extract of *V. negundo* (ALEVN) were tested for its antipyretic activity in New Zealand rabbits. In control group (Group 1), the normal mean rectal temperatures (38.5 ± 0.10) of rabbits were recorded before PGE1 administration. The mean rectal temperature after 30 min of PGE1 injection was $40.3 \pm 0.2^\circ\text{C}$ and $39.8 \pm 0.006^\circ\text{C}$ at the 240 min (4th h). In standard group (Group 2), the mean rectal temperature after 30 min of PGE1 injection was $40.2 \pm 0.118^\circ\text{C}$. After administration of standard drug aspirin, there was a significant ($P \leq 0.05$) decrease in temperature at 30 min, and thereafter, there was a highly significant ($P \leq 0.001$) reduction in temperature from 60 min to 240 min. In Test 1 (Group 3)/*V. negundo* 200 mg/kg, the mean rectal temperature after 30 min of PGE1 injection was $40.3 \pm 0.11^\circ\text{C}$. There was a reduction of temperature significantly ($P \leq 0.05$) at only 240 min (4 h), and in between, temperature was maintained constantly above the set point. In Test 2 (Group 4)/*V. negundo* 400 mg/kg, the initial mean rectal temperature after 30 min of PGE1 injection was $40.38 \pm 0.12^\circ\text{C}$. The significant ($P \leq 0.05$) reduction of temperature was observed from 120 min onward, i.e., $39.8 \pm 0.05^\circ\text{C}$, $39.6 \pm 0.10^\circ\text{C}$ at 150 min, and $39.6 \pm 0.20^\circ\text{C}$ at 180 min. Highly significant ($P \leq 0.001$) reduction was observed at 240 min ($39.1 \pm 0.14^\circ\text{C}$). In Test 3 (Group 5)/*V. negundo* 800 mg/kg, the initial mean rectal temperature after 30 min of PGE1 injection was $40.4 \pm 0.005^\circ\text{C}$. The significant ($P \leq 0.05$) reduction of temperature was observed at 30 min onward to 150 min ($40.1 \pm 0.007^\circ\text{C}$, $40 \pm 0.06^\circ\text{C}$, $39.8 \pm 0.10^\circ\text{C}$, $39.7 \pm 0.15^\circ\text{C}$, $39.5 \pm 0.11^\circ\text{C}$) and thereafter highly significant ($P \leq 0.001$) reduction at 180 and 240 min as follows: $39.2 \pm 0.16^\circ\text{C}$, and $38.6 \pm 0.2^\circ\text{C}$ as depicted in Table 1.

Table 1: The effect of ALEVN on temperature at various time intervals

Groups	Time								
	0 min/normal temperature	30 min after PGE1	30 min after treatment	60 min	90 min	120 min	150 min	180 min	240 min
Control (NS 2 ml/kg)	38.5±0.10	40.33±0.2	40.2±0.04	40.1±0.03	40±0.05	40±0.05	40±0.162	39.8±0.010	39.8±0.06
Standard (aspirin 28 mg/kg)	38.6±0.12	40.2±0.118	39.8±0.21*	39.6±0.14**	39.4±0.14**	39.3±0.09**	39.1±0.16**	38.8±0.14**	38.5±0.10**
<i>V. negundo</i> (200 mg/kg)	38.5±0.1	40.3±0.11	40.2±0.03	40.2±0.033	40.1±0.06	40±0.08	39.9±0.049	39.6±0.205	39.6±0.064*
<i>V. negundo</i> (400 mg/kg)	38.5±0.16	40.38±0.12	40.2±0.11	40.1±0.08	40.1±0.08	39.8±0.05*	39.6±0.10*	39.6±0.205*	39.1±0.14**
<i>V. negundo</i> (800 mg/kg)	38.6±0.08	40.4±0.005	40.1±0.07*	40.0±0.06*	39.8±0.10*	39.7±0.15*	39.5±0.11*	39.2±0.16**	38.6±0.22**

All values are expressed as mean $\pm$ SEM, $n=6$, $^*P < 0.05$, $^{**}P < 0.001$. *V. negundo*: Aqueous leaf extract of *V. negundo*, SEM: Standard error of mean

The Effect of *A. paniculata*

In Test 1 (Group 3)/*A. paniculata* 200 mg/kg, the mean rectal temperature after 30 min of PGE1 injection was $40.3 \pm 0.11^{\circ}\text{C}$. There was no reduction of temperature until 240 min (4 h).

In Test 2 (Group 4)/*A. paniculata* 400 mg/kg, the mean rectal temperature after 30 min of PGE1 injection was $40.4 \pm 0.05^{\circ}\text{C}$. There was no significant reduction of temperature until 120 min, and the significant ($P \leq 0.05$) reduction of temperature was observed at 150 min, which was 39.6 ± 0.08 thereafter highly significant ($P \leq 0.001$). A reduction in temperature was observed from 180 min to 240 min, ($39.4 \pm 0.04^{\circ}\text{C}$ and $39.3 \pm 0.07^{\circ}\text{C}$).

In Test 3 (Group 5)/*A. paniculata* 800 mg/kg, the mean rectal temperature after 30 min of PGE1 injection was $40.4 \pm 0.02^{\circ}\text{C}$. The significant ($P \leq 0.05$) reduction of temperature was observed 90 min onward up to 150 min that was $39.8 \pm 0.09^{\circ}\text{C}$, $39.7 \pm 0.14^{\circ}\text{C}$, and $39.5 \pm 0.12^{\circ}\text{C}$, whereas highly significant ($P \leq 0.001$) reduction was seen at 180 and 240 min as follows $39.3 \pm 0.07^{\circ}\text{C}$ and $39.1 \pm 0.01^{\circ}\text{C}$ as depicted in Table 2.

DISCUSSION

This study proved that the ALEVN and Aqueous leaf extract of *A. paniculata* (ALEAP) showing antipyretic activity in PGE1 induced fever in rabbits. With 400 mg/kg doses, significant antipyretic activity was started with ALEVN at 120 min, whereas it was started at 150 min with ALEAP. With 800 mg/kg doses, significant antipyretic activity was started with ALEVN at 30 min, whereas it was started at 90 min with ALEAP. Thereafter, antipyretic effects were sustained with both the doses in both the plant extracts. These effects were compared to aspirin used as a standard drug.

The mid-brain reticular formation, anterior hypothalamus, and posterior hypothalamus are considered to be the PGE1 febrile sensitive sites involved in the thermoregulatory function.^[19] One more study also indicated same that the site of PGE1, febrile sensitivity resides in the area of the anterior hypothalamus.^[20] This concludes that pyrogen activity in the production of fever is mediated through PGE1. There is a remarkable similarity in the mode of action of PGE1 and pyrogen in the production of fever except in the onset of action which is rapid with PGE1. Hence, pyrogen may be considered as a precursor which produces PGE1 in the brain tissue to affect the febrile response. Therefore, PGE1 coming one step closer to the production of fever would act more rapidly than pyrogen.

V. negundo leaf extract consists of alkaloids, flavonoids, tannin, terpenes, β -sitosterol, proteins, and starch.^[21] Many of these compounds inhibit the PGs and leukotriene synthesis.^[22]

Table 2: The effect of ALEAP on temperature at various time intervals

Groups	Time								
	0 min/normal temperature	30 min after PGE1	30 min after treatment	60 min	90 min	120 min	150 min	180 min	240 min
Control (NS 2 ml/kg)	38.5±0.10	40.33±0.2	40.2±0.044	40.1±0.033	40±0.05	40±0.05	40±0.162	39.8±0.010	39.8±0.06
Standard (aspirin 28 mg/kg)	38.6±0.12	40.2±0.118	39.8±0.207*	39.6±0.14**	39.4±0.14**	39.3±0.09**	39.1±0.16**	38.8±0.14**	38.5±0.10**
<i>A. paniculata</i> (200 mg/kg)	38.5±0.07	40.3±0.109	40.3±0.09	40.2±0.11	40.1±0.07	40.2±0.02	40.19±0.02	39.8±0.05	39.7±0.05*
<i>A. paniculata</i> (400 mg/kg)	38.5±0.07	40.4±0.05	40.2±0.05	40.1±0.02	40.1±0.06	39.9±0.08	39.6±0.08*	39.4±0.0**	39.3±0.07**
<i>A. paniculata</i> (800 mg/kg)	38.6±0.07	40.4±0.02	40.2±0.05	40.1±0.02	39.8±0.09*	39.7±0.14*	39.5±0.12	39.3±0.07**	39.1±0.01**

All values are expressed as mean±SEM, n=6, *P<0.05, **P<0.001. ALEAP: Aqueous leaf extract of *A. paniculata*, SEM: Standard error of mean

All values are expressed as mean $\pm$ SEM, $n=6$, $^*P<0.05$, $^{**}P<0.001$. ALEAP: Aqueous leaf extract of *A. paniculata*, SEM: Standard error of mean

Thus, these active compounds of *V. negundo* may possess anti-inflammatory and antipyretic activity^[23] by reducing the secretion of pro-inflammatory cytokines and tumor necrosis factor alpha.^[24] From our study, we can say that *V. negundo* in high doses reduces temperature very fast, whereas moderate doses reduces temperature slowly. Tirumalasetty *et al.*^[25] reported that alcoholic leaf extract of *V. negundo* produced a significant antipyretic effect. In another study, Miskin *et al.*^[26] proved that petroleum and methanolic extracts of *V. negundo* showed significant antipyretic activity.

The *A. paniculata* consists of steroids, alkaloids, flavonoids, tannins, glycosides, amino acids, saponins, and terpenoids. Like *V. negundo*, these constituents also possess anti-inflammatory and antipyretic activity. According to one study, andrographolide, a major bioactive constituent of the plant, produced a significant antipyretic effect in yeast-induced fever in rats.^[27] Akintola *et al.*^[28] reported that methanolic leaf extract of *A. paniculata* showed significant antipyretic activity in yeast-induced pyrexia model. In another study, ALEAP (as a part of polyherbal formulation) showed maximal antipyretic effect than methanolic extract.^[29] The ethanolic and other solvent extracts of leaves of *Pergularia extensa* showed significant antipyretic activity in rats. This was due to the presence of phytoconstituents such as flavonoids, steroids, and saponins.^[30] The presence of flavonoids was reported in *Dalbergia* species and flavonoids are known to inhibit PG synthase.^[31] Therefore, it appears that the antipyretic action of *Dalbergia* species may be related to the inhibition of PG synthesis in hypothalamus.^[32] The antipyretic property of *Acacia catechu* may be ascribed to the presence of flavonoids.^[33] Some of the flavonoids are predominant inhibitors of COX or lipooxygenase. Thus, flavonoids have antipyretic effects.^[34]

In our study, the probable mechanism of antipyretic action of both the plant extracts may be due to the presence of flavonoids in them, which are responsible for the inhibition of PGs synthesis in the same way as aspirin. In case of *A. paniculata*, delayed and sustained action may be due to the presence of other phytochemicals in that plant. Further phytochemical analysis and pharmacodynamic molecular studies are needed to detect any other phytochemicals apart from flavonoids in the antipyretic action.

CONCLUSION

The study concludes that aqueous extract of *V. negundo* has fast onset and sustained antipyretic action in New Zealand rabbits, whereas *A. paniculata* has delayed onset and sustained antipyretic effect.

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