Antipyretic activity of aqueous extracts of Andrographis paniculata and Carica papaya in Wistar albino rats – A comparative study

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ABSTRACT

Background: Andrographis paniculata (AP) and Carica papaya (CP) are extensively distributed in South India and traditional healers use these plant preparations for treating various disorders including fever. Individual studies on AP & CP have shown that both have anti-pyretic property. However, it is not known what would be the effect when both the extracts are given together. Hence this study was undertaken. Objectives: To evaluate the anti-pyretic activity of aqueous extract of Andrographis paniculata & Carica papaya individually and in combination in rats. To compare the anti-pyretic activity of aqueous extract of Andrographis paniculata & Carica papaya individually and in combination with that of paracetamol in rats. Methods: 48 adult male rats were divided in to 8 groups of 6 animals each. Fever was induced by injecting Brewer’s yeast subcutaneously. Control group received normal saline 10ml/kg, standard group paracetamol 150mg/kg and the 6 test groups received AP 100mg/kg, 200mg/kg, CP 100mg/kg, 200mg/kg and AP with CP 100mg/kg and 200mg/kg. Rectal temperature was measured at baseline, 1, 2, 3, and 4 hours. Results: Individual plant extracts of AP & CP significantly reduced the body temperature when compared to control (P<0.05). The combination of AP & CP 200mg/kg had shown significant reduction in body temperature which was comparable to standard drug paracetamol. CP had better antipyretic activity when compared to AP at 200mg/kg (P<0.05). Conclusion: The combination of both the plant extracts had better antipyretic action compared to individual plant extract and the antipyretic activity of the combination was comparable to paracetamol.

Keywords: Antipyretic activity, Andrographis paniculata, Brewer’s yeast, Carica papaya, Paracetamol

INTRODUCTION: Andrographis paniculata (AP) (Common names - Kalmegh or King of bitters), a member of plant family Acanthaceae, is one of the well-known medicinal ancient plant used by the traditional healers globally. It is native to India, Srilanka, Pakistan, Indonesia and other countries in Sub tropical and South East Asia. Its phytochemical constituents include β-sitosterol, diterpene lactone consisting of andrographolide, 14-deoxyandrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographolide, 19-O-acetylanhydroandrographolide, homoandrographolide, 14-acetylandrograpolide, andrograpanin\(^1\). The primary bioactive component of the plant is Andrographolide and it is present in all the parts of the plant. The plant has been evaluated for its anti-inflammatory, antioxidant, immunostimulant, antipyretic, antimalarial, anthelmintic, antiviral, antibacterial, antihepatitic, anti diarrheal, anti hyperglycemic and anticancer\(^2\) activities. Carica papaya (CP) (Common name - papaya) belonging to Caricaceae family is the most commonly cultivated food crop having a rich source of vitamins, minerals, enzymes and other nutritive compounds\(^3\) making it more valuable for the traditional healers. The bark, leaves, flowers, fruits and seeds are found to possess different chemical constituents such as alkaloids, flavonoids, glycosides, tannins, saponins phenols and steroids\(^4\). It is reported for its anticancer, antimalarial, antiplasmodial, anthelmintic, antifungal, antibacterial, antioxidant & immunostimulant, antisickling, antihypertensive, wound healing, hepatoprotective, antiinflammatory, antifertility, diuretic, hypoglycemic\(^3\), antipyretic\(^5\) activities and also in treatment of dengue fever\(^6,7,8\). With the rapid expansion of fever types, need for development of other alternative medicines including plant preparations become crucial. Both the plants Andrographispaniculata & Carica papaya being cost effective, easily available, non-toxic and extensively cultivated, are recommended by some of state governments in India and by traditional herbal healers either individually and/or in combination with other herbal products for treating fever. The present study aimed to assess the combined effect of this two plants for its anti-pyretic activity which were not evaluated so far.

MATERIALS AND METHODS: The study was conducted after obtaining approval from the Institutional Animal Ethics Committee (IAEC4/Alr.no 24/Dt.12.12.2017). AP and CP plant leaves were collected from kalavaiforest area, Vellore District. 200gm of AP and CP powered leaves were taken separately in a conical flask and 800ml of distilled water was added to it, dissolved and left to stand for 12 hours. The two separate mixture was then filtered using Whatman No.1 filter paper, the filtrates were decocted using water bath at 65 °C for complete evaporation of solvent. The semi solid extracts obtained were collected in an air tight container and
stored at room temperature. About 48 healthy adult male Wistar albino rats weighing 200-250g were used for the experiment. Animals were divided into 8 groups with 6 animals in each group. Each group was housed separately in a clean polypropylene cages at 23 – 25°C with 12 hour alternating light-dark cycle and provided with free access to food and water. On the day of the experiment, the animals were allocated into control and experimental groups (n=6) and were given the control, standard and test drugs per oral. Control group received normal saline 10ml/kg, standard group paracetamol 150mg/kg and the 6 test groups received AP 100mg/kg, 200mg/kg, CP 100mg/kg, 200mg/kg and AP with CP 100mg/kg and 200mg/kg. Digital thermometer was inserted up to 2cms and initial rectal temperature was recorded in all animals. Pyrexia was induced in all 48 animals by subcutaneous injection of 15% Brewer’s yeast suspension (10 mL/kg) at the back below the nape of the neck. After 18 hours, all 48 animals shown to have increase in rectal temperature of about 0.5 to 1°C. Fever induced animals were treated orally with normal saline 10ml/kg, paracetamol 150mg/kg, AP(100,200mg/kg), CP(100,200mg/kg) and the combination AP+CP(100,200mg/kg). Rectal temperature was recorded in extract/drug treated animals in all groups at baseline, 1 h, 2 h, 3 h and 4 hour.

RESULTS: Subcutaneous yeast injection produced pyrexia in all group animals with 1°C mean increase in rectal temperature. The aqueous extracts of both the plants at the given doses were found be safe without toxic effects and had shown to have significant antipyretic activity compared to control (p<0.01) (Table 1). Dose dependant effect was observed in CP and AP+CP combination groups. 2 hours after AP+CP(200mg/kg) administration (p<0.001) and 3 hours after CP(200mg/kg) administration (p<0.01) had better antipyretic effect. The mean reduction in (baseline – 4th hour after drug administration) temperature in standard, AP100&200mg/kg, CP100&200mg/kg and AP+CP 100&200mg/kg was 2.7, 1.72, 1.79, 1.88, 2.37, 2.39, 2.63 respectively (Table 2). The AP+CP(200mg/kg) combination found to be statistically significant when compared to AP 100mg/kg (p<0.05) and also appeared to be comparable with the standard. Whereas AP when compared to CP and AP+CP combination produced less reduction the body temperature.

Table 1: Effect of aqueous extracts of Andrographis paniculata and Curica papaya on body temperature in yeast induced pyrexia.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Temp °C</th>
<th>Temperature, 18 hours after yeast administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 hour</td>
<td>1 hour</td>
</tr>
<tr>
<td>Control</td>
<td>Normal saline 10ml/kg</td>
<td>37.58±0.14</td>
<td>40.08±0.14</td>
</tr>
<tr>
<td>Standard</td>
<td>Paracetamol 150mg/kg</td>
<td>37.4±0.11</td>
<td>40.23±0.10</td>
</tr>
</tbody>
</table>

All Values are expressed as Mean ± SEM. N=6, *p<0.05, **p<0.01 and *** p<0.001 considered as statistically significant compared with control.

1st Hour : a p< 0.05 compared with AP100
2nd Hour: a p<0.001 compared with AP100, b p<0.05 compared with AP200, c, p<0.05 compared with CP100
3rd Hour: a p< 0.05 compared with AP100
4th Hour : a p< 0.05 compared with AP100

**DISCUSSION:** Prostaglandin (PGE2) acts on the thermoregulatory center in hypothalamus of the brain and play a vital role in temperature regulation. Fever due to infection, injury, inflammation, cancer etc., is caused by generation of pyrogens such as ILs, interferons, TNFα which increases the PGE2 levels in hypothalamus and raise the temperature set point\textsuperscript{11}. As such fever is an important sign for the health care providers, as it alerts them to intervene in preventing mortality\textsuperscript{12}. The majority of antipyretic drugs work by inhibiting the COX enzyme involved in prostaglandin synthesis and thereby reduce the PG levels. However these drugs are not free
from toxic effects. In the current study antipyretic activity of AP and CP was evaluated individually and in combination by inducing pyrexia using brewer’s yeast in experimental rats. Pyrogens produced from yeast injection is thought to increase the PG levels which resulted in fever in rats. The aqueous extracts of AP and CP have shown antipyretic activity against brewer’s yeast induced fever in a dose dependent manner. Among the two plant extracts, CP at dose 200mg/kg dose was found to have better antipyretic activity than AP. The results of the combination of the two plant extracts were better than the individual compounds and it was comparable with the standard drug. This indicates that the combination of these two plant extracts have therapeutic effect comparable to that of paracetamol in the treatment of fever and it shall have additional benefit when given along with other antipyretic drugs.

Among many active phytochemical constituents, diterpene lactones and β sitosterol present in AP, flavonoids and β sitosterol present in CP are known to inhibit PG synthesis and also the release of proinflammatory mediators. However andrographolide (diterpene lactone) being less water soluble, explains that aqueous extract of AP couldn’t produce effective fever control compared to CP. The antipyretic action of AP and CP could be due to reduction in prostaglandin levels and proinflammatory mediators.

Thus it can be inferred that the aqueous extracts of AP and CP has significant antipyretic activity compared to control. The aqueous extract of CP has better antipyretic action when compared with AP. The combination of AP and CP at dose 200mg/kg have antipyretic action comparable to the standard drug paracetamol which could be due to the synergetic effects of the active constituents present in both plant extracts. Hence AP and CP can be used as an adjuvant drug to reduce the dose and side effects of other drugs in fever. Whereas the combination of AP and CP can be used as an equivalent drug to other drugs routinely used in treating fever.

CONCLUSION: The present study has shown that aqueous extracts of AP and CP have antipyretic activity. The combination of AP and CP revealed better efficacy comparable to that of paracetamol. CP has better effect compared to AP. The phytochemical constituent diterpene lactones, β sitosterol and flavanoids are known to have antipyretic activity. The mechanism of action can be attributed to inhibition of prostaglandin synthesis. Future studies are required to evaluate its mechanism of action in detail to develop these plant combination as a newer drug to treat fever.

DECLARATIONS

Funding: None
Conflict of interest: Nil

Ethical approval: The study was approved by the Institutional Animal Ethics Committee (IAEC4/Alr.no 24/Dt.12.12.2017).

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