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## Research Article

## A study of anti-inflammatory activity of the benzofuran compound (3,4-dihydro 4-oxo-benzofuro [3,2-d] pyrimidine-2-propionic acid) in chronic model of inflammation

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### ABSTRACT

**Background:** Benzofuran compounds are shown to have pharmacological properties such as antiarrhythmic, antidepressant, antifungal, and antibacterial activity. Some studies conducted on them have revealed that they are having anti-inflammatory property also. Hence, we carried out this study to know whether the benzofuran compound 3, 4-dihydro 4-oxo-benzofuro (3, 2-d) pyrimidine-2-propionic acid has got anti-inflammatory activity against chronic inflammation.

**Methods:** Wistar albino rats were treated with benzofuran compound under study and phenylbutazone in the dose of 100 mg/kg, orally with 2% gum acacia as suspending agent and the effects were observed in chronic experimental model of inflammation namely, cotton pellet induced granuloma model.

**Results:** In the present study, it was shown that the benzofuran compound under study has got significant anti-inflammatory activity against the chronic model of inflammation.

**Conclusion:** Our experiment shows that the benzofuran compound under study has got significant anti-inflammatory activity and may, as well become an additional anti-inflammatory drug if further studies are conducted in this direction involving human beings.

**Keywords:** Benzofurans, Phenylbutazone, Chronic inflammation, Cotton pellets, Granuloma

### INTRODUCTION

Inflammation is the local reaction of vascularized tissue to injury.<sup>1</sup> Inflammation has two themes, inflammation and repair. Inflammation serves to destroy, dilute, or wall off the injurious agent and the tissue that it may have destroyed. Repair begins during the active phase of inflammation but reaches completion after the injurious agent has been neutralized.

The process of inflammation comprises of series of events involving acute and chronic responses to all forms of injury. Acute inflammation is of short duration lasting for few minutes to 1 or 2 days. Chronic inflammation is of longer duration and is associated histologically with the presence of lymphocytes, macrophages, and proliferation of small blood vessels and fibroblasts.

Clinically, chronic inflammation may follow acute inflammation because of persistence of injury causing

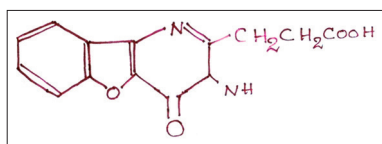
stimulus. Or it may also be due to repeated bouts of acute inflammation. A number of endogenous natural substances such as prostaglandins, leukotrienes histamine, and serotonin released during tissue injury have been incriminated as mediators of inflammation.<sup>1</sup>

Benzofurans are compounds with heterocyclic ring structure where in a benzene ring is fused with a furan ring. These compounds do possess significant antiarrhythmic,<sup>2</sup> antidepressant,<sup>3</sup> antifungal,<sup>4</sup> antibacterial,<sup>5</sup> and properties. They also have been shown to have anti-inflammatory property.<sup>6,7</sup> Hence, we took up this study to know if the benzofuran compound “3, 4-dihydro 4-oxo-benzofuro (3, 2-d) pyrimidine-propionic acid” has got any anti-inflammatory activity in the chronic model of inflammation.

### METHODS

The under study compound “3, 4-dihydro 4-oxo-benzofuro (3, 2-d) pyrimidine-propionic acid” is a white solid, insoluble

in water. Its structural formula is as follows:



This compound was synthesized by Dr. Y. Agasimundin, Reader in Chemistry at Gulbarga University, Gulbarga, in the Chemistry Laboratory of Gulbarga University, Gulbarga.

Phenylbutazone,<sup>8</sup> a pyrazolone derivative, a potent anti-inflammatory drug was used as standard drug. This drug was obtained from Pacific Pharmaceuticals Pvt. Ltd., Bengaluru, Karnataka, India.

Both the above mentioned drugs were administered orally in the dose of 100 mg/kg with 2% gum acacia as a suspending agent with the help of a polythene tube. 2% gum acacia was used as a control drug.

### Animals

Adult Wistar albino rats of either sex of average weight 150-200 g which were in-bred in the Central Animal House of Vijayanagara Institute of Medical Sciences, Ballari, Karnataka, India were used for the study. They were allowed standard rat chow pellet and water ad libitum both being withdrawn just before the study. The animals were kept in a polypropylene cage under standard conditions in dim light and noise free room. The study was done after getting the Clearance of Institutional Animal Ethical Committee.

Cotton-wool pellet implantation model of chronic inflammation; the rats were divided into three groups of six each, one group received the test drug, i.e., benzofuran 100 mg/kg, another group received the standard drug phenylbutazone 100 mg/kg. Both the drugs were given as suspensions of 2% gum acacia, and the other group acted as control which received 2% gum acacia. All the drugs were administered orally.

Uniform cotton wool pellets weighing 10 mg each were prepared and sterilized with 70% ethyl alcohol. The rats were anesthetized with pentobarbitone sodium administered in the dose of 35 mg/kg body wt., intraperitoneally. Subsequently with aseptic precautions small incisions of about 1 cm each in length were made on either side in the flanks on the ventral aspect of rats and the sterilized pellets were implanted in the subcutaneous plane, in all, 4 pellets were implanted in each rat. Wounds were then sutured and rats were kept in the cage individually after recovery from anesthesia.

The drugs were given 1 hr before implantation and subsequently once daily orally for four consecutive days.

The animals were sacrificed on the 5th day and the pellets were removed, cleared of extraneous tissue and dried in a hot air oven to a constant weight. The dry weight of granuloma formed on the pellets was determined by noting the difference in dry weights of cotton pellets recorded before and after the implantation in respective groups.

The percent of anti-inflammatory activity was determined by the formula;

$$[W_c - W_t / W_c] \times 100$$

Where  $W_c$  is the mean dry weight of granuloma in control group,  $W_t$  is the mean dry weight of granuloma in drug treated group.

### Statistical analysis

All the data obtained were presented as mean and standard error of mean, the data were analyzed using Student's *t*-test.

## RESULTS

In our study, it was demonstrated that there was a significant reduction in the amount of granuloma formation in the under study group than the control group. That is the benzofuran compound under study exhibited significant anti-inflammatory activity as compared to the control group, with  $p < 0.05$  (Table 1 and Figure 1).

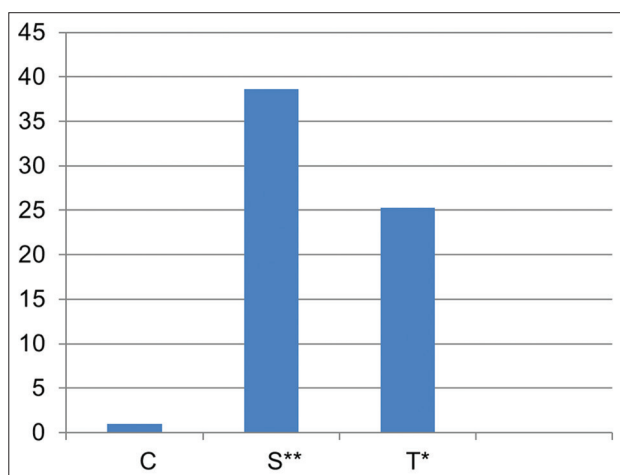
## DISCUSSION

Phenylbutazone a potential anti-inflammatory agent was the main stay for the treatment of inflammatory disorders of various degrees of different kinds of durations stretching from acute to sub-acute and chronic inflammatory disorders, mainly involving major and minor joints which are crippling the individuals with deformities and physical impairments irrespective of the age and sex. It so happens in the olden and debilitated individual's life a nightmare for them. In these conditions, the onus and emphasis being done on going in for patient friendly, gut friendly, economical, cost benefited and free from any of the side effects that endangers the individuals was the need for looking into the ideal anti-inflammatory

**Table 1: Effect of different drugs on granuloma dry weight.**

Drugs	Mean granuloma dry weight (mg)±SEM	Percentage inhibition
Control	13.56±0.87	-
Phenylbutazone (standard)	8.32±0.58**	38.64
Benzofuran (test drug)	10.13±0.54*	25.29

\*\*High significant -  $p < 0.01$ . \*Significant -  $p < 0.05$ . SEM: Standard error mean



**Figure 1: Bar chart illustrating the percent of inhibition (anti-inflammatory activity) in cotton pellet induced granuloma. y - axis indicates percent of inhibition. C - Control, S - Standard drug (phenylbutazone), T - Test drug (benzofuran). \*\*Highly significant -  $p < 0.01$ , \*Significant -  $p < 0.05$ .**

drugs. In this scenario focus is being done on newer molecules with their potential actions, in this endeavour our efforts were made sincerely to identify the potential anti-inflammatory activity in these benzofuran compounds being compared with phenylbutazone a standard anti-inflammatory drug. This study throws an insight into the possible anti-inflammatory activity in these group of compounds augurs further in-depth studies to be considered as potential anti-inflammatory agent.

Inflammation is a defensive response mechanism of the body against harmful injurious stimuli like physical trauma, chemicals, thermal injury, or infections etc. The process of inflammation is mediated by mediators such as prostaglandins leukotrienes, histamine, serotonin, and bradykinin.

Inflammation is a necessary process that is needed to ward off the injury causing stimuli, but needs to be controlled as it is associated with symptoms like pain. One way of controlling inflammation is by inhibiting the prostaglandin and leukotrienes synthesis. This can be done by inhibiting the enzymes cyclooxygenases and lipoxygenases.<sup>9</sup>

As mentioned in the results, our study demonstrated that the test drug benzofuran has got significant anti-inflammatory activity in chronic model of inflammation. This can be explained on the basis that the benzofurans are inhibitors of both lipoxygenases and cyclooxygenases enzymes.<sup>10</sup> The benzofuran compound under study also has a acid moiety attached to it, this also aids in abetting the anti-inflammatory activity of the parent benzofuran.<sup>10</sup> The parent benzofuran compound has been fused with the pyrimidine moiety also, in the under study compound, and this fusion of pyrimidine moiety to benzofuran compound inhibits the metalloproteinases.<sup>11</sup> These metalloproteinases have been implicated as mediators of inflammation.<sup>12</sup> All these things are responsible for the anti-inflammatory activity shown by the test benzofuran compound.

## CONCLUSION

With our study, we conclude that the above mentioned benzofuran compound has got significant anti-inflammatory activity and it could, as well become one of the anti-inflammatory drug if proper further studies are carried out using different dosage profiles.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Animal Ethics Committee*

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