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Anti Inflammatory Activity of Flavone and its Hydroxy Derivatives - A Structure Activity Study

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FLAVONE and its various mono hydroxy derivatives were synthesised by adopting standard procedures and investigated for their anti- inflammatory activity in carrageenin - induced paw edema (acute) and Cotton pellet granuloma in rats (chronic). In the acute study flavone and its 2', 4', 3 and 6-hydroxy derivatives exhibited a dose related anti-inflammatory activity. In chronic study also flavone and its hydroxy derivatives were found to exert a similar degree of inhibition against inflammation. The present results have been correlated with the analgesic activity of these compounds reported earlier. In general, the dose required to produce significant anti-inflammatory effect was higher when compared to their analgesic dose. The activity of hydroxy flavones have been compared with the anti-inflammatory activity of corresponding methoxy derivatives of flavone, reported earlier. It has been observed that, hydroxylation favours anti- inflammatory activity of flavone nucleus more than methoxylation.

The anti-inflammatory potential of many naturally occurring flavonoid compounds has been well documented[1-4]. Recently, in an attempt to study the structure activity relationship of flavonoids, several methoxy derivatives of flavone were synthesised and investigated for their anti-inflammatory activity[5]. In the present study some hydroxy derivatives of flavone have been synthesised and subjected to anti-inflammatory screening. Some of these compounds have already been reported to possess varying degree of analgesic activity[6].

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MATERIALS AND METHODS

Flavone Derivatives

The following derivatives of flavone were synthesised in our laboratory adopting standard procedures: Flavone[7], 3- hydroxy[8], 6-hydroxy[9] 2'-hydroxy[10] and 4'- hydroxy[11] flavones. The purity of all the compounds was established by melting point, chromatography with authentic samples, (Bio-Organics, Madras) elemental analysis, UV and IR spectroscopy.

Drug Preparation

All the flavonoid compounds were prepared as a uniform suspension in 1% carboxy methyl cellulose (CMC) for animal experiments. The dose selection of the test compounds was based on the results of analgesic study reported earlier[6].

Anti-inflammatory Screening

Acute inflammation : Carrageenin-induced hind paw edema in rats[12] :

Male wistar albino rats (120 - 150 g) were used in the study, carrageenin 0.1 ml (1% Solution) was injected s.c. into plantar surface of the right hind paw. The test compounds (12.5, 25, 50 or 100 mg/kg) were administered to different groups of animals (n=6) 30

TABLE - I

EFFECT OF FLAVONE DERIVATIVES ON ACUTE INFLAMMATION

Treatment/Dose	Difference in Paw Volume (ml) 12.5mg/kg	25mg/kg	50mg/kg	100mg/kg
Flavone	—	1.0±0.07	0.73±0.07*	0.6±0.09*
3-Hydroxy Flavone	0.72±0.07*	0.68±0.10*	0.58±0.06**	—
6-Hydroxy Flavone	0.78±0.03*	0.73±0.09*	0.52±0.05**	—
2'-Hydroxy Flavone	—	0.88±0.15	0.81±0.09*	0.75±0.14*
4'-Hydroxy Flavone	—	1.07±0.08	0.9±0.07*	0.68±0.13*

Each value represents the mean ± SEM of six observations.

* $p < 0.05$, and ** $p<0.01$ compared with vehicle treated group (Paw volume : 1.2 ± 0.09) volume of paw edema in phenylbutazone (100mg/kg) treatment was 0.3 ± 0.01**.

min prior to carrageenin injection. The paw volume was measured four hours after carrageenin injection using a plethysmograph. The difference between the left and right paw was taken as a measure of edema. Any significant reduction in the volume of the paw compared to the control group was considered as anti-inflammatory response.

Chronic inflammation (Cotton pellet granuloma)[13]:

Male Wistar albino rats (150 - 200 g) were used in this study. Sterile cotton pellets were implanted s.c. under light ether anaesthesia. Separate groups of animals (n=6) were treated with flavone or its derivatives for seven days in different doses (12.5, 25, 50 or 100 mg/kg, s.c.). On the eighth day, the animals were sacrificed and the cotton pellets were removed with the adhering granulation tissue. Pellets were dried at 50°C for 24 h and weighed. Any significant reduction in the weight of cotton pellets compared to the control group was considered as anti- inflammatory response.

In both acute and chronic study, a group of animals treated with phenyl butazone (100 mg/kg s.c.) was used for comparison and the control animals received the vehicle (CMC). All the results were analysed by ANOVA followed by DUNNET'S 't' test.

RESULTS

Acute inflammation

In control animals a significant difference in paw volume was observed between the left and right paw which was an indication of edema. In Phenylbutazone treated animals the volume of the inflammed paw was significantly reduced. Similar results were observed in rats treated with flavone, 3-hydroxy, 6-hydroxy, 2'- hydroxy and 4'-hydroxy flavones (**Table 1**).

Chronic inflammation

The weight of cotton pellets was significantly reduced after phenylbutazone treatment.

Similarly, a significant reduction in the weight of cotton pellets was observed after treatment with flavone and its hydroxy derivatives. However, there was no further reduction in the weight of cotton pellets with increasing doses.

DISCUSSION

Synthesis

The flavone derivatives were mostly synthesised by conventional methods by adopting standard procedures except a few modification with a view to

TABLE - II

EFFECT OF FLAVONE DERIVATIVES ON CHRONIC INFLAMMATION

Treatment/Dose	Weight of Cotton Pellets (mg) 12.5mg/kg	25mg/kg	50mg/kg	100mg/kg
Flavone	-	30.16±1.01*	29.8±1.38*	27.3±0.84*
3-Hydroxy Flavone	33.1±1.16*	32.2±0.76*	29.25±0.93*	—
6-Hydroxy Flavone	34.72±1.7*	33.2±0.76*	32.40±1.2*	—
2'-Hydroxy Flavone	—	29.21±0.54*	27.30±0.92*	27.23±1.89*
4'-Hydroxy Flavone	—	31.25±1.36*	29.57±0.68*	28.56±0.92*

Each value represents the mean ± SEM of six observations.

* $p < 0.05$, compared with vehicle treated group (Weight of Cotton Pellet : 42.95 ± 2.95 mg).

weight of cotton pellet in phenylbutazone (100mg/kg) treatment was 22.10 ± 0.25**.

reduce the time consumed or to increase the yield or purity of the compounds.

Anti-inflammatory activity

The present results indicate that, the compound flavone has potent anti-inflammatory activity in acute inflammation which is in agreement with the earlier report[5]. Hydroxylation at 3 and 6 position of flavone has potentiated the anti-inflammatory activity of flavone as observed by greater reduction in paw edema even at lower doses. Hydroxylation at 2' and 4' positions has slightly reduced the anti-inflammatory activity of flavone (Table I).

In the chronic model of inflammation substitution of hydroxyl group at the above positions of the flavone nucleus has not significantly altered the anti-inflammatory potential of flavone. (**Table II**).

Comparison with methoxy derivatives of flavone

The methoxy derivatives of flavone has been reported to possess varying degree of anti-inflammatory activity[5]. The following observations can be made by comparing the results of hydroxy flavones and their corresponding methoxy derivatives[5].

1. In general, hydroxy derivatives of flavone are more potent anti-inflammatory agents than their corresponding methoxy derivatives.

2. This is further supported by the observation that a flavonoid glycoside such as gossypin[2] and Kaempferol[14], which contain many hydroxyl groups in their flavone skeleton have potent anti-inflammatory activity.

3. Methoxylation at 4' position[5] has totally abolished the activity of flavone while hydroxylation has conferred potent anti-inflammatory activity.

Correlation with analgesic activity

The Flavone compounds which are found to exhibit significant anti-inflammatory activity in the present study have already been reported to possess potent analgesic activity[6]. In general, a significant anti-inflammatory response for these compounds could be observed only at higher doses in comparison to the dose required for analgesia[6].

Further investigation of polyhydroxy flavones will definitely help in identifying safe and effective compounds against pain and inflammation.

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