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Original Research Article

Evaluation of antihistaminic activity of quercetin by using histamine induced bronchospasm and clonidine induced catalepsy models

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ABSTRACT

Background: Histamine is an important mediator of allergic reactions. Even though presently available antihistaminics are effective in treatment of allergic reactions, still there is scope for better new drugs. Quercetin has been used as a nutritional supplement and may be beneficial against a variety of diseases. Some of the beneficial effects include anticancer, antitumor, anti-ulcer, anti-allergy and anti-inflammatory effects. As quercetin is used in traditional system of medicine for treatment of allergies, this study was undertaken to evaluate antihistaminic activity of quercetin.

Methods: In histamine induced bronchospasm model, 18 guinea pigs were divided into 3 groups. Control group received normal saline, standard control group received Chlorpheniramine and test group received Quercetin. All drugs were given once daily for 5 days. Preconvulsive dyspnoea was calculated on day 0 and day 5 for all guinea pigs after administration of Histamine aerosol. In clonidine induced catalepsy model, 18 albino mice were divided into 3 groups. Control group, standard control group and test group received normal saline, Chlorpheniramine and Quercetin respectively. One hour after administration of drugs the mice were given clonidine and catalepsy was measured at 30, 60, 90, 120 and 150 min.

Results: In histamine induced bronchospasm model, both chlorpheniramine and quercetin produced significant protection as compared to control group. In clonidine induced catalepsy model the effect of quercetin was comparable to chlorpheniramine.

Conclusions: Quercetin has significant antihistaminic activity. It appears to be due to H1 receptor blockade, contrary to the belief that it inhibits release of histamine from mast cells.

Keywords: Antihistaminic, Clonidine, Chlorpheniramine, Histamine, Quercetin

INTRODUCTION

Histamine is an important mediator of allergic reactions. It causes bronchoconstriction, airway hyper-responsiveness and airway inflammation in allergic asthma.[1,2] It induces secretion of mucus that is responsible for airways oedema and contraction of airway smooth muscle.[3] Histamine stimulates macrophages recruitment, epithelial and smooth muscle hyperplasia in the alveolar area that causes airway inflammation.[4] It is released during early and late phase of allergic reaction.[5] Allergic reactions and allergic asthma are very common in developing countries. Even though presently available antihistaminics are effective in treatment of allergic reactions still there is scope for better new drugs.

Quercetin belongs to the class called flavonols that cannot be produced in the human body. Quercetin is said to be one of the most widely used bioflavonoids for the treatment of metabolic and inflammatory disorders. The highest concentrations of flavonols are found in vegetables such as onions and broccoli, fruits such as apples, cherries, and

berries and drinks such as tea and red wine. It has been used as a nutritional supplement and may be beneficial against a variety of diseases. Some of the beneficial effects include cardiovascular protection, anticancer, antitumor, anti-ulcer, anti-allergy, anti-viral, anti-inflammatory activity, anti-diabetic, gastroprotective effects, antihypertensive, immunomodulatory and anti-infective.[6]

Quercetin exerts anti-allergic effects by inhibiting the release of histamine from mast cells.[7,8] Quercetin's ability to prevent allergic effects has tremendous implications for the treatment and prevention of asthma and bronchitis. The cell membranes of mast cells which have been known to be an immune gateway to the brain as well as the environment and emotional stress.

As quercetin is used in traditional system of medicine for treatment of allergies, this study is undertaken to evaluate antihistaminic activity of quercetin.

METHODS

The protocol was approved by Institutional animal ethics committee. The drugs used in this study were Histamine hydrochloride (Sigma-Aldrich Ltd) which was used as bronchial spasmogenic agent, Clonidine (Unichem laboratory) used as cataleptic agent, Chlorpheniramine maleate (Alkem Ltd.) used as standard antihistaminic agent, Quercetine (Sisco Research Laboratories) used as test drug.

Histamine induced bronchospasm was induced by exposing the animals to 0.25% histamine aerosol in Histamine chamber (24×14×24 cm perplex glass chamber).[9] Preconvulsive dyspnoea (PCD) which was the time (in sec) of histamine aerosol exposure to the onset of dyspnoea leading to the appearance of convulsion was taken as end point. PCD was noted for each animal. As soon as Preconvulsive dyspnoea was noted the animals were removed from the chamber and placed in fresh air to recover.

Prior to drug treatment, PCD was calculated for each animal in all three groups. 18 inbred guinea pigs (400-600 gm) of either sex were divided into 3 groups with 6 animals each.

Group I (Control) received 2 ml normal saline orally once daily for 5 days and on 5th day, 2 hrs after administration of normal saline Histamine aerosol was given and PCD was calculated.

Group II (Standard control) received Chlorpheniramine Maleate 2 mg/kg orally once daily for 5 days and on 5th day, 2 hrs after administration of Chlorpheniramine maleate, Histamine aerosol was given and PCD was calculated.

Group III (Test) received Quercetin 50 mg/kg orally once daily for 5 days and on 5th day, 2 hrs after administration of quercetin, Histamine aerosol was given and PCD was calculated.[10] Percentage protection (% protection) was calculated by using the formula:

$$\text{Percentage protection} = (1\text{-}T1/T2) \times 100.$$

Where; T1 = the mean of PCD before administration of test drugs. T2 = the mean of PCD after administration of test drugs.[9]

Clonidine-induced catalepsy in mice were done by Bar test which was used in this model. After administration of clonidine to the mice the forepaws of mice were placed on a horizontal bar (1 cm in diameter, 3 cm above the table) and the time required to remove the paws from bar, which gives duration of catalepsy (in seconds) was noted for each mice.[11,12] 18 Albino mice were divided into 3 groups (n=6).

Group A (Control group) received single dose of normal saline 10 ml/kg orally, Group B (Standard control) received single dose of Chlorpheniramine maleate 10 mg/kg orally, and Group C (Test group) received single dose of Quercetin 50 mg/kg orally.

All the groups were received clonidine 1 mg/kg subcutaneously, 1 hr after the drug administration. The duration of catalepsy was measured at 30, 60, 90, 120 and 150 min.[13]

Statistical analysis

For histamine induced bronchospasm, the results were expressed as mean±SD, the pre-treatment PCD (day 0) and post treatment PCD (day 5) values within the group were compared using paired t test. P <0.05 was considered statistically significant. The post treatment PCD values (day 5) between the groups were compared by using unpaired t-test. P <0.05 was considered statistically significant.

For clonidine induced catalepsy, the results were expressed as mean±SD and analyzed for statistical significance using one-way ANOVA followed by Tukey test. p< 0.05 was considered statistically significant.

RESULTS

Histamine induced bronchospasm in guinea pigs

Table 1 shows the comparison of 0 day and 5th day PCD values within the groups. It was highly significant for standard group (p <0.0001) and for test group (p <0.001), but it was statistically not significant for control group (p >0.05). Table 2 shows the inter group comparison of 5th day PCD values. It was highly significant for standard control group when compared to control and test groups (p <0.0001). It was also highly significant for test group on comparing with control group (p <0.0001).

Table 1: Comparison 0 day and 5th day PCD in all three groups.

Parameter	Group I		Group II		Group III	
	Day 0	Day 5	Day 0	Day 5	Day 0	Day 5
Mean	92.83	95.0	94.83	476.50	95.83	123.33
SD	4.71	6.48	5.04	25.78	5.34	6.662
SEM	1.92	2.65	2.06	10.53	2.18	2.70
Percent protection	2.28		80.09		22.29	
p-value	0.46		<0.0001		< 0.001	

Day 0 and 5th day PCD values within the groups were compared using paired t test, n=6, P-value <0.05 was considered statistically significant.

Figure 2: Comparison of day 5 PCD values.

Parameter	Group I	Group II	Group III	P-value		
				I vs II	I vs III	II vs III
Mean	95.00	476.50	123.33	<0.0001	<0.0001	<0.0001
SD	6.48	25.78	6.62			
SEM	2.65	10.53	2.70			

The post treatment PCD values (day 5) of each group was compared with other groups by using unpaired t test, n=6, p-value <0.05 was considered statistically significant.

Clonidine induced catalepsy in mice

Table 3 shows comparison of duration of catalepsy at 30 min. The reduction in duration of standard group and test group were highly significant on comparing to control group (p <0.0001) where as it was statistically significant for standard control group when compared to test group (p <0.05).

Table 3: Comparison of duration of catalepsy at 30 min.

Group	Mean duration (sec)	SD	ANOVA
A	98.33	5.08	F=506.6 P<0.0001
B	35.17* **	3.65	
C	42.17*	1.83	

The results were analysed by One-way ANOVA followed by Tukey test, n=6, F=506.6, p <0.0001, *p <0.0001 compared to control (group A), **p <0.05 compared to test group (group C).

Table 4: Comparison of duration of catalepsy at 60 min.

Group	Mean duration (sec)	SD	ANOVA
A	136.0	8.67	F=538.6 P<0.0001
B	42.83*	3.97	
C	47.0*	1.26	

The results were analysed by one-way ANOVA followed by Tukey test, F=538.6, p <0.0001, *p <0.0001 compared to control (group A).

Table 4 shows comparison of duration of catalepsy at 60 min. The reduction in duration of standard group and test group were highly significant on comparing to control group (p <0.0001) where as it was statistically not significant when standard control group was compared to test group.

Table 5 shows comparison of duration of catalepsy at 90 min. The reduction in duration of standard group and test group were highly significant on comparing to control group (p <0.0001) where as it was statistically not significant when standard control group was compared to test group.

Table 5: Comparison of duration of catalepsy at 90 min.

Group	Mean duration (sec)	SD	ANOVA
A	166.7	6.47	F= 1372 P<0.0001
B	48*	3.34	
C	53.33*	2.42	

The results were analysed by one-way ANOVA followed by Tukey test, n=6, F=1372, p <0.0001, *p <0.0001 compared to control (group A).

Table 6 shows comparison of duration of catalepsy at 120 min. The reduction in duration of standard group and test group were highly significant on comparing to control group (p <0.0001) where as it was statistically not significant when standard control group was compared to test group.

Table 6: Comparison of duration of catalepsy at 120 min.

Group	Mean duration (sec)	SD	ANOVA
A	115.20	10.53	F= 256 P<0.0001
B	39.17*	3.14	
C	45.45*	2.16	

The results were analysed by one-way ANOVA followed by Tukey test, n=6, F=256, p <0.0001, *p <0.0001 compared to control (group A).

Table 7 shows comparison of duration of catalepsy at 150 min. The reduction in duration of standard group and test group were highly significant on comparing to control group ($p < 0.0001$) where as it was statistically significant for standard control group when compared to test group ($p < 0.05$).

Table 7: Comparison of duration of catalepsy at 150 min.

Group	Mean duration (sec)	SD	ANOVA
A	83.17	5.11	F= 382.7 P<0.0001
B	34.0* **	2.0	
C	39.83*	1.94	

The results were analysed by one-way ANOVA followed by Tukey test, n=6, F=382.7, $p < 0.0001$, *$p < 0.0001$ compared to control (group A), **$p < 0.05$ compared to test group (group C).

DISCUSSION

The present study was undertaken to evaluate the possible antihistaminic role of quercetin. In the histamine induced bronchospasm model, significant increase in preconvulsion duration ($p < 0.001$) was observed in both standard group and test group as compared to control group (Table 2). It indicates significant antihistaminic property of Quercetin even though chlorpheniramine maleate produced significant increase in preconvulsion duration compared to it. In a study conducted by Jung CH et al, it was shown that quercetin inhibits histamine release from mast cells and helpful in treatment of allergic asthma.[14] In this study, also the antihistaminic activity was significant, but it appears to be due to blockade of H1 receptors as this model test the ability to block H1 receptors.

Clonidine an α2 adrenoreceptor agonist induces catalepsy by release of histamine from mast cells. Clonidine induced catalepsy is inhibited by mast cell stabilizing agents and histamine H1 receptor antagonists.[15] In this study, it was found that both quercetin and chlorpheniramine maleate reduced duration of clonidine induced catalepsy significantly as compare to control group and there was no statistical significance between these two groups at 60, 90 and 120 minutes (Table 4, 5 and 6). This indicates that the inhibitory effect of quercetin on clonidine induced catalepsy is comparable to that of chlorpheniramine maleate. Results of this model indicates that the test compound quercetin has significant antihistaminic activity but cannot precisely tell whether it is because of inhibition of histamine release from mast cells or due to H1 receptor blockade but, as it has shown H1 receptor blockade property in histamine induced bronchospasm model, it appears to be due to H1 receptor blockade.

CONCLUSION

Quercetin has significant antihistaminic activity. It appears to be due to H1 receptor blockade, contrary to the belief that it inhibits release of histamine from mast cells.

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