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Assessment of the bronchodilator effect of "2-(2,3-dihydroxyphenyl)-4-ethylchroman-3,5,6-triol" isolated from *Ficus trichopoda (*Baker, 1883) (MORACEAE) leaves

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Abstract

This study aims to investigate the mechanism(s) implicated in the bronchodilation effect exerted by "2-(2,3-dihydroxyphenyl)-4-ethylchroman-3,5,6-triol"isolated from *Ficus trichopoda* (Kaker, 1883) (MORACEAE) leaves. This molecule was isolated from ethyl acetate extract fraction followed by chromatography. It was tested on isolated trachea of guinea pig pre contracted with histamine 10 µM. injected in the bath in a cumulative manner, this molecule relaxes completely the organ with EC_{50} of $9{,}74.10^{-7}$ M. Pre incubating the organ in a bath containing the isolate at concentrations of $4.81.10^{-5}$ M, $9.62.10^{-5}$ M, $1.44.10^{-4}$ and $1.92.10^{-4}$ M induces a right shift of the concentration effect curves of histamine with an increase of histamine EC_{50} from $5.62.10^{-7}$ M in the absence of the isolate to $5.81.10^{-6}$, $6.91.10^{-6}$, $7.92.10^{-6}$ and $8.1.10^{-5}$ M in its presence ($p<0.05$). These results indicate a competitive antagonism between histamine and the isolate.

Keywords: Bronchodilator; *Ficus Trichopoda;* Guinea Pig; *In Vitro*; Trachea

1. Introduction

Asthma is one of the most common chronic diseases; it presents different features including bronchoconstriction, airway hyperreactivity, mucus secretion, and chronic inflammation. Its symptoms include episodes of wheezing, coughing, and breath shortness [1]. The World Health Organization (WHO) estimates that asthma affects more than 339 million persons, both children and adults, across the world regardless the level of development [2].

According to the Global Initiative of Asthma (GINA), the treatment of asthma aims to control symptoms to minimize risk of exacerbations [3]. Numerous compounds have been developed to management it. They act as bronchodilators or prevent airway inflammation [4].

Even though current anti asthmatic drugs have proven to be effective, some are associated with side effects. For instance, used for a long period, inhaled corticosteroids may be accompanied by bronchitis, nasopharyngitis, and respiratory tract infection [5,6]. While, anticholinergic drugs can cause dry mouth, because they can reduce saliva production, blurred vision, resulting from their impact on the muscles controlling the eye's lens. Some individuals may also experience urinary retention or constipation, as these compounds can affect the bladder and intestines smooth muscles [7]. On the over hand beta 2 can increased heart rate, provokes headache, dizziness and anxiety or shakiness [8].

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Furthermore, these drugs are sometimes not accessible to many patients, mainly in poor countries, due to their high cost or the luck of infrastructure (roads, medical centres or drugstore). Herbal medicines are widely used in those countries. Indeed, according to the WHO, at least 80 % of African populations rely on traditional herbal medicine for their primary healthcare due to its accessibility and affordability [9]. For the safety of the users, effectiveness of traditional medicines needs to be proven, their toxicity should be checked. It is in these axes that we bring our contribution to investigate the bronchodilator effect of *Ficus trichopoda* leaves which are largely used in the high plateau of Madagascar as anti-asthmatic.

In our previous studies, we have already proven, *in vivo*, that the hydro alcoholic extract of the leaves of this plant protects the experimental animals from dyspnoea induced by histamine [8]. While *in vitro* tests have demonstrated its broncho dilatory activity. We also have identified a broncho dilator compound from those leaves [10] dernier article. On the basis of the mentioned scientific evidences, the present study was undertaken to investigate the mechanism of action involved in the bronchodilation induced by this compound.

2. Materials and methods

2.1. Isolate preparation

The isolate used in this work was obtained from chromatography of ethyl acetate fraction of *Ficus trichopoda* leaves. It was identified as 2-(2,3-dihydroxyphenyl)-4-ethylchroman-3,5,6-triol (we have coded MR23 this isolate) [10] reference du dernier article.

2.2. Drugs and chemicals

Dichloromethane, ethyl acetate and methanol (analytical grade) used in isolation of the molecule used in this work were purchased from LABOSI, 141 Rue de JAVEL, Paris 75. Histamine and ingredients used for making Krebs Henseleit solution were obtained from Sigma-Aldrich Inc. (St. Louis, MO, USA). Chromatographic preparative plates (Ref 4856-840) were purchased from MERK (39 Rte Industrielle de la Hardt, 67120 Molsheim, France).

2.3. Animal of experimentations

Guinea pigs, of either sex, weighing between 250 and 300 g were used in the present study. They were placed under standard laboratory conditions: room temperature of 22 ± 2ºC and free access to tap water *ad libitum* and commercial standard diet., with 12/12 hours cycle of light and darkness at the animal house of LPGPC (Laboratory of General Pharmacology, Pharmacokinetic and Cosmetology of the Science Faculty of Antananarivo, Madagascar). Care and use of the animals were approved by the bioethics committee of the Sciences Faculty, University of Antananarivo, Antananarivo, Madagascar, registered as CE/Fac Sciences/08/2025

2.4. Preparation of the isolated trachea

Animals were deprived of food 12 hours prior experiments, with free access of water. They were euthanized, using thiopental sodium at the dose of 50 mg/kg, injected intramuscular (Pentothal Sodium, Abbott, Turkey), and the neck was incised to remove the trachea. After carefully washing the trachea, it was placed in Krebs solution at room temperature and aerated with carbogen. It was cut into strips of 3 - 5 mm and mounted in organ bath maintained at 37°C and aerated with carbogen, under 1 g tension [11].

2.5. Assessment of the bronchodilator activity of the isolate

Isolated organ was allowed to equilibrate for 45 minutes, during which the organ bath was renewed every 15 minutes. After equilibrium period, histamine was injected in the bath in to get 10 µM. At maximal contraction, the isolate (coded MR23) was injected in the bath in a cumulative manner from 4.81×10^{-5} M until complete relaxation of the organ. Relaxation-concentration curve of the isolate was traced in semilogarithmic scale, its EC_{50} was evaluated by linear regression using the middle part of the curve [12].

2.6. Elucidation of the isolate mechanism of action

The isolated trachea was preincubated in organ bath containing the isolate at concentrations of $4.81.10^{-5}$ M, $9.62.10^{-5}$ M, $1.44.10^{-4}$ and $1,92.10^{-4}$ M respectively before contracting with histamine injected in the bath in a cumulative manner until maximal contraction. Curves representing contraction-concentration of histamine in the absence and presence of the isolate at different concentrations were traced in semilogarithmic scale, its EC_{50} was evaluated by linear regression using the middle part of the curves [12].

2.7. Statistical Analysis

The data were converted into a computerized database format and expressed as mean with standard error of the mean. Two-way ANOVA was used for multiple comparisons between the means to detect the statistical significance using Excel (version 6). Statistic significance was considered when p-value was ($p<0.05$), using "t" test of Student.

3. Results

Injected cumulatively in an organ bath containing isolated tracheal preparations precontracted with histamine (10 µM), the isolate produced a progressive relaxation of the tissue, beginning from a final concentration in the bath of $4.81.\ 10^{-5}$ M. The relaxant effect was concentration-dependent and reached a maximal response of 100% at $2.8.\ 10^{-4}$ M (Figure 1). The relaxant responses were significant as compared to the total pre-constricted state ($p < 0.05$). The EC_{50} value, calculated by linear regression of the linear portion of the concentration–effect curve, is equal to $1.5.\ 10^{-4}$ M. These findings demonstrate that the isolate exhibits significant bronchodilator activity.

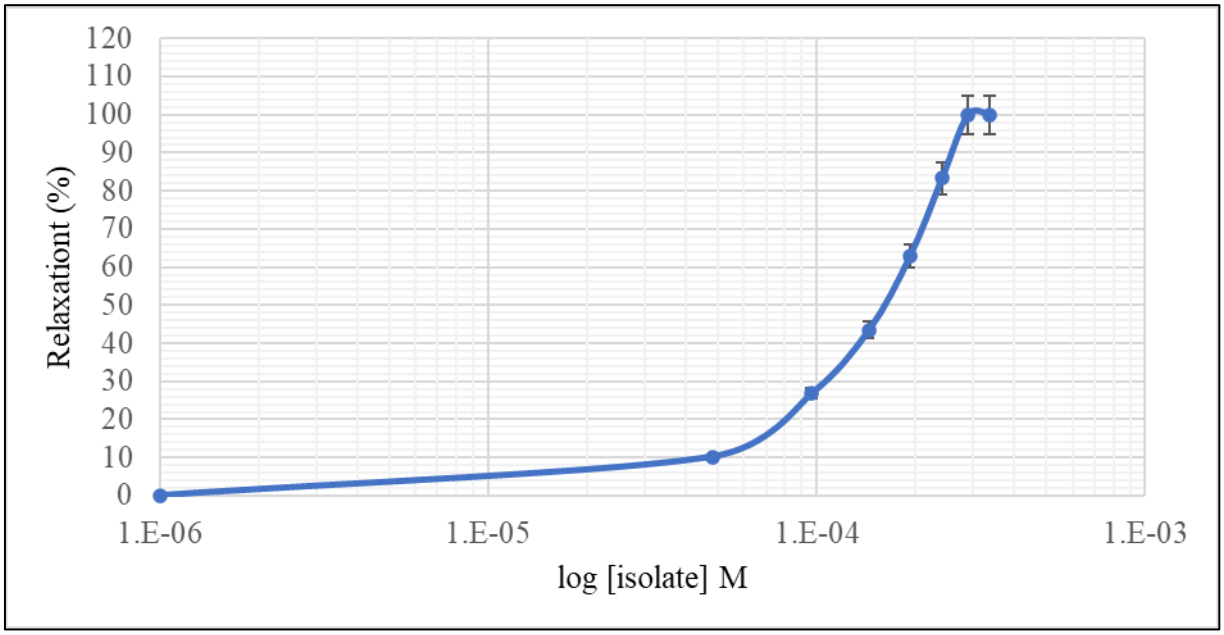

Figure 1 Relaxation of isolated trachea induced by the isolate injected, in a cumulative manner, in the bath containing the isolated trachea precontracted by histamine 10 µM ($\bar{x} \pm esm$; n=10; $p<0.05$)

3.1. Isolate mechanism of action

Incubation of the isolated trachea in a bath containing MR23 at increasing concentrations prior to contraction with histamine caused a rightward shift of the histamine concentration–response curves, with an increase of its EC_{50}, while maintaining the maximal contraction amplitude. In the absence of MR23, histamine added cumulatively in the bath induced 100 % contraction of the isolated trachea, with an EC_{50} of $9.74.\ 10^{-7}$ M. After pre-incubation of the trachea in a bath containing increasing concentrations of MR23, histamine still produced a maximal (100 %) contraction of the tissue; however, its EC_{50} increased to $5.62.\ 10^{-7}$, $5.81.\ 10^{-6}$, $6.91\ .10^{-6}$, $7.92.10^{-6}$, and $8.1.\ 10^{-5}$ M in the presence of MR23 at concentrations of $4.81.10^{-5}$, $9.62.\ 10^{-5}$, $1.44.\ 10^{-4}$ and $1.92.\ 10^{-4}$ M, respectively (Figure 2). These results are characteristic of competitive antagonism, indicating that MR23 acts as a competitive antagonist of histamine at H_1 receptors in the isolated guinea pig trachea. After calculation pA2 and Kd of this isolate are respectively equal to pA2 ≈ 4,82 and Kd ≈ $1,5.\ 10^{-5}$ M.

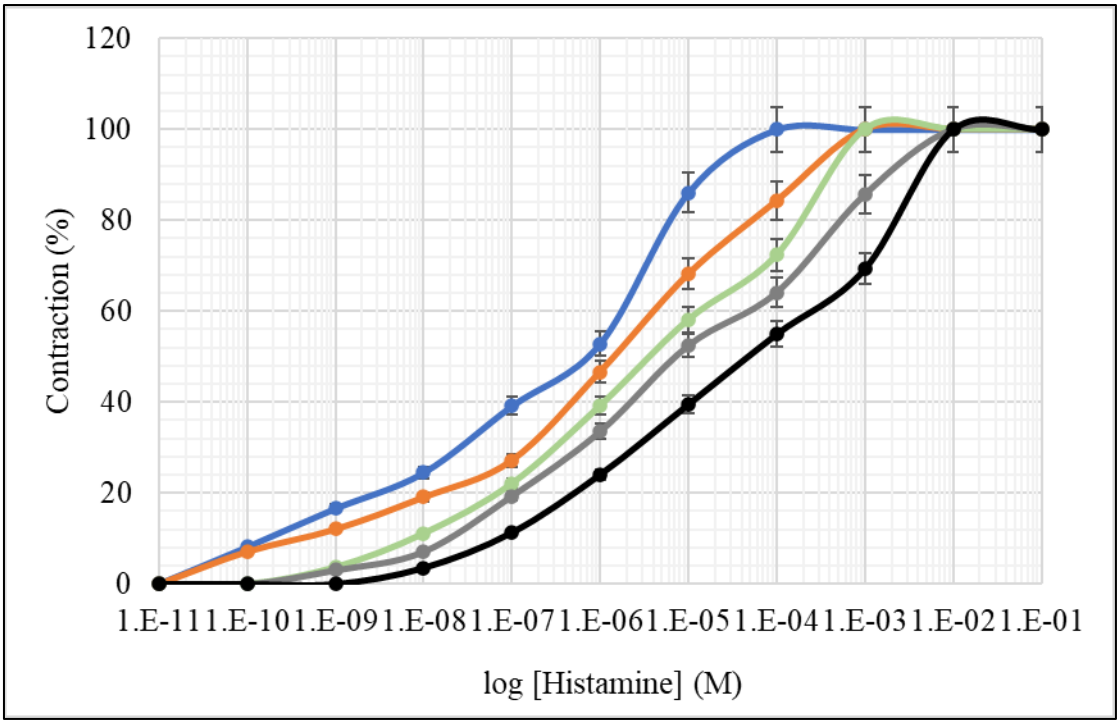

Figure 2 Concentration-response curves for the constriction effect of histamine on tracheal muscle in absence and presence of the isolate from *Ficus trichopoda* leaves at concentrations of 4,81.10^{-5}M 9,62.10^{-5}M , 1,44.10^{-4}M and 1,92.10^{-4} M ($\bar{x} \pm \bar{\sigma}$; n=10; p<0,05)

4. Discussion

The results of ethnobotanical survey that we have conducted in the high plateau of Madagascar, indicate that *Ficus trichopoda* leaves are used to relieve breathing difficulties, one of asthma symptoms. Our previous results have shown that hydro alcoholic extract of the leaves protects the experimental animals from dyspnoea induced by histamine and relaxes the isolated trachea pre contracted by histamine [9]. To identify a molecule involved in this activity and to elucidate its mechanism of action, a bioassay fractioning followed by chromatography was undertaken leading to isolation of a bronchodilator molecule, "2-(2,3-dihydroxyphenyl)-4-ethylchroman-3,5,6-triol"which belongs to the flavonoid family, more specifically to the flavanol subclass [10].

The present study demonstrates that this isolate relaxes histamine-induced contraction of guinea pig tracheal preparations. Pre-incubation of the trachea with the isolate produced a rightward shift in the histamine concentration–response curve, with an increased EC_{50} while maintaining maximal contraction. This pharmacological profile is characteristic of competitive antagonism, indicating that the isolate binds reversibly to H_1 receptors, preventing histamine from activating the Gq/PLC/IP_3/DAG signalling cascade. Inhibition of this pathway prevents the rise of intracellular calcium levels that normally triggers smooth muscle contraction. Because there is no IP_3-mediated calcium release from the sarcoplasmic reticulum, leading to reduced activation of myosin light chain kinase (MLCK) and limited actin–myosin interactions, thereby decreasing smooth muscle contraction. This cascade ultimately produces relaxation of the smooth muscle, contributing to bronchodilation resulting in improved airflow. The pA_2 value of approximately 4.82 and Kd of 1.5×10^{-5} M reflect moderate affinity of H1 receptor and support this interpretation. These values indicate that the isolate reduces tissue sensitivity to histamine without impairing the maximal contractile response, a characteristic of competitive antagonists.

Although much of the current evidence relies on *in silico* docking and predictive models, some flavonoid-type compounds have been investigated for their potential to act as histamine H_1 receptor antagonists. Computational studies suggest that flavonoids such as quercetin, kaempferol and sophoflavescenol for instance can bind to the H_1 receptor's ligand-binding site, indicating possible competitive antagonism by occupying the receptor and inhibiting histamine-induced signalling [13, 14]. Experimental studies further support that flavonoids can reduce H_1 receptor activity and histamine-induced contraction *in vitro*, such as alpha-mangostin [15]. Collectively, these findings suggest

that flavonoid structures may serve as natural competitive H_1 antagonists, providing a mechanistic basis for their traditional use in managing respiratory disorders, including asthma.

In addition to receptor-level antagonism, the isolate displayed direct relaxant activity, producing complete, concentration-dependent relaxation of precontracted tracheal tissue. This effect suggests action downstream of receptor activation, possibly through modulation of intracellular calcium influx, activation of cAMP/PKA or cGMP/PKG pathways, or opening of potassium channels to hyperpolarize smooth muscle [16, 17]. The dual action—both receptor antagonism and direct smooth muscle relaxation—may enhance overall bronchodilation.

Supporting these *in vitro* findings, hydro alcoholic extract of the leaves of *Ficus trichopoda*, source of this isolate, protects experimental animals from histamine-induced dyspnoea. This observation aligns with the traditional use of this plant as an anti-asthmatic remedy, providing ethnopharmacological validation of the isolate's potential therapeutic benefits. Bronchodilators represent a cornerstone of therapy in respiratory medicine, offering symptomatic relief and improving lung function in patients with asthma, COPD, and other airway diseases.

5. Conclusion

In summary, the findings suggest that the isolate combines competitive H_1 receptor antagonism with potent bronchodilator activity, offering a mechanistic explanation for both its experimental efficacy and its traditional medicinal use. Further studies should investigate its intracellular targets in more detail, assess its efficacy *in vivo*, and evaluate safety profiles to explore its potential as a novel anti-asthmatic agent.

Compliance with ethical standards

All experiment were carried out in the Laboratory of General Pharmacology, Pharmacokinetic and Cosmetology at the Sciences Faculty, University of Antananarivo, Madagascar. Care and use of the animals were approved by the bioethics committee of the Sciences Faculty, University of Antananarivo, Antananarivo, Madagascar, registered under number CE/Fac Sciences/08/2025

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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