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Investigation And Evaluation of Various Parameters of the Anti-Asthmatic Pharmacological Activity of Araucaria Columnaris Leaf Extracts

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ABSTRACT

The study of botanical extracts to determine their antiasthmatic properties has gained attention in recent years. The current study used asthma models to examine the antiasthmatic properties of Araucaria columnaris leaf extract. The significance of A. columnaris Hook. for the treatment of asthma is unknown, despite the fact that it is notable for its profusion of bioactive chemicals that are derived from flavonoids, phenolics, terpenoids, steroids, and tannins. The effects of the leaf extract on milk-induced leukocytosis and catalepsy were the main subjects of the investigation.

The ethanolic extract derived from the leaves of Araucaria columnaris (350mg/Kg) significantly mitigated catalepsy induced by clonidine and haloperidol in mice, indicating a possible antihistaminic effect.

Furthermore, the ethanolic extract (350mg/Kg) has shown a statistically significant decrease in both total leukocyte and eosinophilia counts in a dose-dependent manner, suggesting its potential anti-allergic and anti-eosinophilic properties.

This research adds to the investigation of natural treatments for asthma, highlighting the significance of A. columnaris as an antiasthmatic agent.

Keywords: *Anti-Asthma, Araucaria columnaris, Anti-allergy, Respiratory infection, Inflammation.*

1. INTRODUCTION

The term "asthma" originates from a Greek word that translates to 'breathless' and refers to a chronic inflammatory disorder of the lungs, marked by bronchial obstruction and inflammation (Vos et al., 2020). This condition frequently results in symptoms as wheezing, difficulty breathing, a feeling of chest tightness, and coughing, especially during the night or in the early morning (Wang et al., 2023). Various factors can trigger it, including allergens (such as pollen, animal dander and dust mites,), respiratory infections, air pollution, physical exertion, and certain medications (Kiley et al., 2007). Asthma is classified as a heterogeneous disease, indicating that it presents differently in different individuals and can range in severity from mild intermittent symptoms to severe persistent symptoms that greatly affect daily activities and necessitate continuous medical treatment (Singh et al., 2016).

Traditional approaches to managing asthma frequently result in adverse side effects and create obstacles for patient adherence. Worldwide, asthma continues to be a major factor in morbidity and mortality, with the World Health Organization indicating an annual death rate of 180,000 linked to the disease, especially common in low- and middle-income nations. In India specifically, estimates indicate that between 15 to 20 million people are affected by asthma. Likewise, in the U.S., around 8.4% of the population suffers from this condition, whereas the global prevalence is reported to be 4.3%.

In the field of alternative medicine, the genus Araucaria, which comprises evergreen coniferous trees, has been historically employed for a variety of medicinal applications, such as treating kidney ailments, respiratory infections, and facilitating wound healing (Aslam et al., 2014). Notably, Araucaria columnaris (G. Forst.) Hook. is distinguished by its rich array of bioactive compounds, which include derivatives of flavonoids, phenolics, terpenoids, steroids, and tannins. Traditionally,

this species has been utilized for its antifungal, antidepressant, antihypertensive, anticancer, respiratory infection healing, anti-inflammatory, and anticoagulant properties (Pavani et al., 2014). Interestingly, the traditional applications of Araucaria columnaris do not encompass asthma treatment, and the antiasthmatic effects of its extract remain unexplored. Nevertheless, research on other plant extracts such as Murraya Koenigii L., Apium graveolens, Argemone Mexicana, Wrightia tinctoria, Carissa opaca, Azadirachta indica, and Luffa cylindrica, which exhibit similar biological activities, has revealed antiasthmatic effects (Verma et al., 2013). These investigations have underscored the inhibition of catalepsy and leukocytosis, alongside broncho-relaxant effects, which are pertinent in asthma models. Specifically, the ethanolic extract of Azadirachta indica and Wrightia tinctoria demonstrated notable antihistaminic activity, while the hydroalcoholic extract of Luffa cylindrica leaves showed potential anti-asthmatic properties (Prakash et al., 2019). These results indicate that further exploration of the antiasthmatic characteristics of A. columnaris, including its impact on catalepsy and leukocytosis, could be valuable for understanding its potential therapeutic applications.

2. MATERIAL AND METHODS

Collection and Authentication of *A. columnaris*

Select plant materials were procured from local vendors and also collected from the botanical garden of Bhopal in March 2024 from Madhya Pradesh State, India. This month, plants initiate flowering and fruiting in India, hence being usually noticed as enriched with phytoconstituents.

Preparation of plant extract

The fresh leaves were initially separated and thoroughly washed under running tap water for one minute, followed by a rinse with distilled water. They were then shade-dried at room temperature until fully dehydrated. The dried leaves were ground into a fine powder and subsequently passed through a 10-mesh sieve to achieve a smooth consistency. A total of 500 grams of this powdered material was stored in a cool, dry location until the extraction process. For extraction, the finely powdered leaves underwent Soxhlet extraction utilizing petroleum ether and ethanol at a temperature range of 60-80°C (Patial et al., 2021).

Experimental Animals

Studies on antihistamine activity were performed using adult Swiss mice, both male and female, weighing between 21-35 g. The animals were sourced from the central animal facility. They were housed under a 14-hour alternating cycle of light and darkness, with relative humidity maintained at 61-75% and a constant temperature of 25 ± 1 °C. During the experimental duration, the mice were given a daily supply of rodent pellets and had unlimited access to tap water. The housing conditions complied with rigorous hygienic standards, ensuring a clean and controlled environment conducive to the welfare of the experimental subjects. The experimental protocol received approval from the IAEC.

Acute toxicity studies

The acute toxicity assessment of A. columnaris was performed in accordance with OECD guidelines 423, and the LD50 was calculated accordingly (Suvarna et al., 2020). The animals underwent a fasting period during which food was withheld overnight, although water was provided. After the fasting duration, the animals were weighed, and the ethanol extract of A. columnaris was administered in a single dose within a range of 150, 300, 600, 1200, 2400, and 4800 mg/kg via gavage using specially designed oral tubes for mice. Continuous monitoring of the animals was conducted for the initial three hours, with a specific focus on any toxic indicators such as salivation, acute convulsions, coma, heightened motor activity, or mortality. Behavioral observations of the animals were carried out both before and after administration, covering a total observation period of 24 hours. Furthermore, the treated animals were observed for an additional 14 days.

Assessment of Anti-cataleptic Activity

A total of two groups comprising thirty-six healthy adult Swiss mice, evenly split between males and females, were arranged into six distinct groups for the purpose of experimentation. One group was exposed to Clonidine-induced catalepsy, while the other was subjected to haloperidol-induced catalepsy. The initial group from each set functioned as the normal control, receiving solely the vehicle (Normal saline). The second group, designated as the disease control, was given 2 mg/kg of Clonidine or haloperidol through intraperitoneal injection. The third group, which served as the standard group, was administered a standard control. The remaining groups, identified as treatment groups AC1, AC2, and AC3, received doses of the ethanolic extract of AC leaves at concentrations of 150, 250, and 350 mg/kg, respectively. The bar test, also known as the hindlimb splay test, was performed, and the duration of immobility, or the time taken to remove the forepaws from a horizontal bar, was measured in seconds. The assessment of Clonidine or haloperidol-induced catalepsy was conducted at intervals of 30, 60, 90, 120, 150, and 180 minutes, with measurements recorded in minutes (Balvinder et al., 2022).

leucocytosis and eosinophilia in mice (Milk-induced)

The animals were divided into 5 distinct groups, each comprising 6 individuals. The first group, designated as the control, was administered a 2% Tween-80 solution, whereas the second group was treated with the standard medication

dexamethasone at a dose of 60 mg/kg. The other groups, labeled AC1, AC2, and AC3, received ACL extract at doses of 150, 250, and 350 mg/kg, respectively. Following a 30-minute treatment period, all groups were injected with boiled and cooled milk at a dosage of 5 ml/kg via subcutaneous route. Total leukocyte and eosinophil counts were measured prior to drug administration and again 24 hours post milk injection (boiled and cool milk at 5 ml/kg). The difference in total eosinophil and leukocyte counts before and 24 hours after drug administration was calculated (Ramdas et al., 2021).

Statistical analysis

Statistical analysis was conducted, and the results are presented as mean ± SEM. One-way ANOVA was employed to assess statistical significance. A significance threshold of $P < 0.05$ was deemed significant.

3. RESULTS

Acute toxicity of the weights of animals and selected organs

The total yield obtained from extraction was found to be 36 % of *A. columnaris* dry leaves weight. No mortality or morbidity indicators were observed at the 2400 mg/kg dose level, while at 4800 mg/kg, two deaths occurred. Other observations include no convulsions, absence of locomotion, and presence of certain behaviours like sniffing, rearing, and grooming during 14 days of observation. Additionally, there were no signs of hair loss, excess urination, or fecal elimination. Consequently, dosages of 150 mg/kg (1/16th of the 2400 mg/kg dose) and 250 mg/kg (1/8th of the 2400 mg/kg dose) and 350 mg/kg (1/5th of the 2400 mg/kg dose) were selected for further investigation (Table 1).

Table 1: Toxicity Study for 2400 mg/kg dose

S. No	Parameters	Inferences
1.	Mortality	2400 mg/kg: zero death, 4800 mg/kg: 2 death
2.	% of Mortality	0 %
3.	Animate Percentage	100%
4.	Convulsion	- (absent)
5.	Locomotion	- (absent)
6.	Sniffing	7 Hrs Period: + (Present), remaining days: - (absent)
7.	Rearing	7Hrs Period: + (Present), remaining days: - (Absent)
8.	Grooming	5 Hrs Period: + (present), remaining days: - (absent)
9.	Hair loss	- (absent)
10.	Excess urination	- (absent)
11.	Excess Feces elimination	- (no)

Catalepsy (Clonidine-induced)

The experiment investigated the impact of *A. columnaris* (AC) ethanol extract on Clonidine-induced catalepsy. Chlorpheniramine maleate significantly reduced catalepsy duration at all time points compared to the control. AC treatment at doses of 150, 250, and 350 mg/kg showed varying degrees of reduction in catalepsy duration compared to the control. The highest dose of AC (350 mg/kg) exhibited the most pronounced reduction, particularly at earlier time intervals (15 and 30 minutes). Efficacy slightly diminished over time but remained significant compared to the control group. Overall, AC shows potential anti-cataleptic properties, with the highest dose (350 mg/kg) achieving notable reductions, warranting further mechanistic studies and dosage optimization (Table 2).

Table 2: Impact of Ethanolic Extract of Araucaria columnaris on Clonidine-Induced Catalepsy

Treatment	Dose (mg/kg)	Duration of Catalepsy (sec)						
		15 min	30 min	60min	90 min	120 min	150 min	180 min
Normal saline	1 ml/kg	30.4± 1.14	89.2 ± 3.38	136.69 ± 1.34	148 ± 5.63	193.27 ± 6.94	221.1 ± 9.68	133.54 ± 1.23
Control (Clonidine)	2 ml/kg	30.8 ± 1.88	90.4 ± 5.57	136.10 ± 2.26	150 ± 9.28	195.98 ± 11.19	209.7 ± 13.03	133.91 ± 2.10
Standard (Chlorpheniramine maleate)	10	11.4 ± 1.44**	32.2 ± 4.30**	113.27 ± 1.78**	53 ± 7.25**	69.32 ± 9.80**	79.0 ± 12.44**	113.15 ± 1.55**
AC	150	27.4 ± 4.95	78.2 ± 14.85	132.92 ± 5.65	128 ± 20.75	142.67 ± 22.72	194.1 ± 26.68	130.20 ± 4.23
AC	250	19.4 ± 4.53*	56.2 ± 11.59*	123.71 ± 5.16*	93 ± 18.65*	105.14 ± 20.59*	124.4 ± 23.0*	120.74 ± 4.79*
AC	350	17.4 ± 3.61*	50.3 ± 8.84*	120.43 ± 4.18*	83 ± 14.15*	95.25 ± 14.48*	105.60 ± 18.90*	118.56 ± 3.81*

Catalepsy (Haloperidol-induced)

In the control group that received only Haloperidol, the duration of catalepsy varied from 9.75 ± 1.308 to 248.5 ± 8.458 seconds, which indicates a significant induction of catalepsy. In contrast, the standard treatment with Tween 80 resulted in a reduced duration of catalepsy, ranging from 11.25 ± 0.085 to 154 ± 3.525 seconds, particularly evident at later time points. The introduction of AC at doses of 150, 250, and 350 mg/kg demonstrated varying levels of attenuation in catalepsy duration. Importantly, the higher doses showed more pronounced effects, with catalepsy duration ranging from 13.25 ± 0.984 to 49.75 ± 5.031 seconds for AC 1 and AC 3, respectively. These findings imply a potential anti-cataleptic effect of AC, with increased doses exhibiting greater efficacy in alleviating catalepsy induced by Haloperidol (Table 3).

Table 3: Activity of haloperidol-induced catalepsy, ethanolic extract of *A. columnaris*

Drug treatment	**Dose**	**15 min**	**30 min**	**60 min**	**90 min**	**120 min**
Normal saline		12.75 ± 1.632	10.75 ± 1.707	7.75 ± 1.188	8.5 ± 0.837	8.5 ± 1.433
Control (haloperidol)	2 ml/kg	9.75 ± 1.308	208.45 ± 4.0	249.6 ± 6.486*	248.5 ± 8.458	245.55 ± 6.915
Standard (Tween 80)	2 ml/kg	11.25 ± 0.084	154 ± 3.525*	142.75 ± 6.58*	109.45 ± 4.85*	78.8 ± 5.869*
AC 1	150	13.25 ± 0.984	98.5 ± 7.255**	89.25 ± 5.212**	74 ± 4.683**	35.995 ± 4.708**
AC 2	250	9.464 ± 1.6345	67.13 ± 5.720**	55.345 ± 7.184**	44.45 ± 3.262**	28.36 ± 0.2875**
AC 3	350	12.25 ± 1.34765	49.75 ± 5.031**	44.25 ± 4.2115**	35.5 ± 3.739**	23.5 ± 2.749**

Additional research is required to investigate the mechanism of action and identify the specific compounds that contribute to the anti-asthmatic effects of A. columnaris leaves.

Leucocytosis in mice (Milk-induced)

The control group (Only vehicle) recorded a total leukocyte count of 2703.12±148.93 cells per cubic millimeter. The standard treatment with dexamethasone resulted in a markedly lower count of 403.42±26.73 cells per cubic millimeter (**p<0.01**), which underscores its effectiveness in diminishing leukocyte levels. Among the experimental groups, AC 1 presented a count of 1544.73±64.59 cells per cubic millimeter (*p<0.05*), AC 2 indicated 689.20±22.28 cells per cubic millimeter (**p<0.01**), and AC 3 revealed 439.72±12.73 cells per cubic millimeter (**p<0.01**), all of which exhibited significant reductions in comparison to the control (Table 4).

Eosinophilia in mice (Milk-induced)

The control group recorded a total eosinophil count of 189.02±37.02 cells per cubic millimeter. The administration of standard treatment with dexamethasone led to a significant decrease in this count, bringing it down to 75.76±9.31 cells per cubic millimeter (**p<0.01**). In the experimental groups, AC 1 presented a count of 116.32±28.61 cells per cubic millimeter (*p<0.05*), AC 2 showed 95.87±9.88 cells per cubic millimeter (**p<0.01**), and AC 3 recorded 87.55±21.48 cells per cubic millimeter (***p<0.001**), all indicating significant reductions when compared to the control (Table 4).

Table 4: Effect of ethanolic extract of *A. columnaris* on leukocyte and eosinophil count

Treatment	**Dose (mg/kg)**	Difference in total leukocyte count (Per cu mm) (Mean± SEM)	Difference in total eosinophile count (Per cu mm) (Mean±SEM)
Control (2% Tween-80 solution)	2 ml/kg	2703.12±148.93	189.02±37.02
Standard (dexamethasone)	50	403.42±26.73**	75.76±9.31**
AC Treated Group 1	150	1544.73±64.59*	116.32±28.61*
AC Treated Group 2	250	689.20±22.28**	95.87±9.88**
AC Treated Group 3	350	439.72±12.73**	87.55±21.48***

(*, **, and *** denote statistically significant differences from the control group, represented by group I, with * indicating p<0.05, ** indicating p<0.01, and *** indicating p<0.001.)

4. DISCUSSION

We observed a dose-dependent anti-cataleptic effect of the ethanolic extract of AC against clonidine. For example, extracts from Nardostachys jatamansi showed a decrease in cataleptic scores caused by metoclopramide, which is attributed to its antioxidant properties and the enhancement of biogenic amines (Aleem et al., 2016). In a similar vein, extracts from the seeds and pulp of Momordica dioica displayed inhibition of catalepsy (clonidine-induced), potentially owing to their antihistaminic effects (Maharudra et al., 2011). Furthermore, the ethanolic extract of Catunaregam spinosa fruits revealed a significant decrease in cataleptic scores induced by clonidine, indicating possible antihistaminic effects (Mahesh et al., 2008). In contrast, the bark extract of Ficus bengalensis also inhibited clonidine-induced catalepsy, likely due to its antihistaminic properties as well (Sandra et al., 2022).

Our research underscores the efficacy of AC ethanol extracts in alleviating Haloperidol-induced catalepsy in a dose-dependent manner. Extracts from the plants Phaseolus vulgaris, Tagetes lucida, Prunus armeniaca L., and Myrica esculenta stem bark have demonstrated encouraging effects on Haloperidol-induced catalepsy (Ragavendra et al., 2016).

Consequently, AC extract may enhance motor functions and neurotransmitter levels, diminish oxidative stress, restore biochemical parameters, and inhibit histamine-induced catalepsy in affected mice. Collectively, these results indicate that these plant extracts possess potential in mitigating catalepsy induced by Clonidine and Haloperidol in animal models, suggesting possible therapeutic advantages in neurodegenerative diseases.

We observed a notable decrease in leukocytosis and eosinophilia (milk-induced) in mice in a dose-dependent manner. AC3 (350mg/Kg) yielded the most favorable outcomes for both conditions. The methanolic and aqueous extracts of Albizzia lebbeck and Syzygium cumin roots exhibited a significant reduction in milk-induced leukocytosis in both rats and mice, indicating their potential anti-allergic properties (Ragavendra et al., 2016). The extract of Gunnera perpensa enhanced milk

production in rats and affected leukocytosis, likely through the development of lobuloalveolar cells and contraction of myoepithelial cells (Simelane et al., 2012). Furthermore, extracts from Solanum melongena leaves and B. variegata stem bark significantly reduced eosinophilia (milk-induced) in mice (Naik et al., 2013). These results suggest that plant extracts can effectively alleviate eosinophilia triggered by milk, emphasizing their potential in addressing conditions related to eosinophilic inflammation.

5. CONCLUSIONS

The antiasthmatic properties of the leaf extract from Araucaria columnaris were examined in models of asthma. This investigation concentrated on the extract's impact on catalepsy and leukocytosis induced by milk. The findings underscored the promise of Araucaria columnaris leaf extract as an adjunctive treatment for asthma, offering scientific validation of its advantageous effects in alleviating asthma symptoms, particularly in addressing allergic reactions.

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