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Quisqualis indica Linn.: HRLCMS/MS profiling and anti-asthma activity of leaf extracts

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Abstract

Background Asthma is a chronic inflammatory disorder of the airways, involving various cells and cellular elements precisely eosinophils, mast cells, neutrophils, T lymphocytes, epithelial cells, and macrophages. Worldwide, about 300 million people are affected by asthma, and is expected that 100 million people may get affected, in 2025. *Quisqualis indica* is commonly planted as an ornamental plant in India; and has medicinal uses. Therefore, the petroleum ether (60–80 °C) LPE and methanolic extract LME of the *Quisqualis indica* leaves were analyzed for anti-asthmatic activity by mast cell degranulation and Milk induced eosinophilia and leukocytosis in mice.

Results It was found that *Quisqualis indica* leaf extracts exhibited protection against the degranulation of mast cells and a reduction in the difference count of leucocytes and eosinophils. LPE and LME (400 mg/kg) have shown 33% and 63% of mast cell protection. LME has shown the most significant mast cell stabilizing action comparable with the standard drug. The extracts decreased the difference count of leucocytes and eosinophils. LME (400 mg/kg) has shown a difference in eosinophil count and a decrease in leukocyte count most comparable with the standard Dexamethasone. Methanolic extract analyzed for phytochemicals by High Resolution Liquid Chromatography Mass Spectroscopy /Mass Spectroscopy method showed the presence of various Phyto-compounds.

Conclusion From the analysis of methanolic leaf extract of *Quisualis indica* revealed the presence of phytocompounds such as Apigenin7-glucoside, Gallic acid, Quercetin, Quercitrin, Kaempferol, etc. The significant decrease in eosinophil and leukocyte count in animals might be due to the higher content of Tannin and flavonoids. A reduction in leukocyte and eosinophil is regulated by type 1 hypersensitivity and adaptogenic factors hence *Quisqualis indica* is effectively helpful in allergy conditions like asthma.

Keywords *Quisqualis indica*, Eosinophil, Leukocyte, Mast cell, Apigenin7-glucoside, Gallic acid, Asthma

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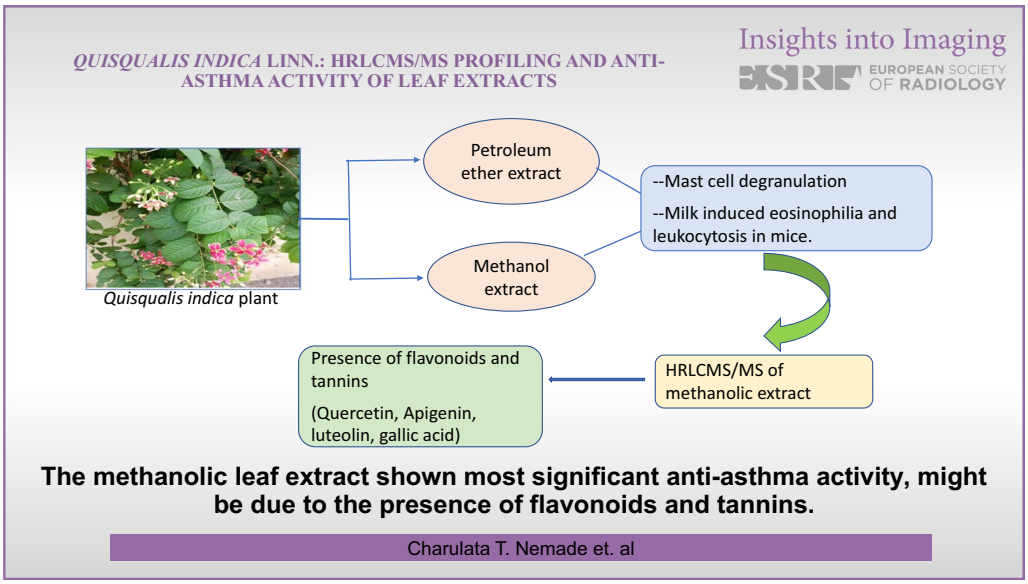
Graphical abstract



Background

Asthma is a chronic inflammatory disorder of the airways, involving various cells and cellular elements, precisely eosinophils, mast cells, neutrophils, T lymphocytes, epithelial cells, and macrophages. Asthma is characterized by hindrance of airflow due to inflammation, bronchospasm, and increased airway secretions. [1] About 300 million people worldwide suffer from asthma, and by 2025, it's predicted that 100 million more will likely develop the condition. The prevalence, severity, and mortality of asthma are greatly affected by geographical variation. Asthma incidence is greater in high revenue countries, and maximum death caused by asthma happens in low middle revenue countries [2].

The multifaceted condition known as asthma is brought on by complex relationships between the environment and heredity. The pathophysiology of this condition includes intermittent airflow restriction, bronchial hyperresponsiveness (BHR), inflammation of the airways and bronchial remodeling. Depending on the severity of the condition, bronchodilators and anti-inflammatory medications can be used to treat asthma. Then, additional treatments are still required to better control asthma, and herbal remedies may be a viable substitute for current synthetic medications [3]. Additionally, plant polyphenols are potent components of natural foods and herbal medicine that have anti-inflammatory, antioxidant, and anti-allergic properties. Previous studies have demonstrated the anti-inflammatory effects of resveratrol, genistin, luteolin, and quercetin, as well as their multiple targets, multiple links, and comprehensive coordination [4].

The plant *Quisqualis indica* Linn*. (Combretaceae)* is an evergreen plant planted in homes and gardens of countries like India, China, Australia, the Amazonian region in Peru, and Pakistan. It is a large sub-woody climber shrub with 3–8 m long branches. Leaves are simple, oppositely having an oblong-elliptic to elliptic shape. It bears the inflorescence with white to pink-colored flowers. Flowers appear in constant succession in sagging clusters with a sweet scent [5, 6].

The leaves of *Quisqualis indica* were used to isolate four crystalline components, which were later identified as nicotinic acid and methylbetaine (trigonelline), L -proline, L -asparagines and potassium quisqualate [7]. Triterpenoids, flavonoids and tannins were isolated from the petroleum ether and methanolic extract of leaf and flower, respectively [8]. Ethno-pharmacologically, the flowers, fruit, seeds, leaves, stem and roots of the plant are used. Leaves are used to relieve pain caused by fever. Leaves decoction is given for flatulent distension and pain in the abdomen. Leaf juice is used to heal boils and ulcers [9]. Fruits and seeds are used in folk medicine as anthelmintic, anti-emetic, and anti-diarrhoea [10].

Different parts of plant have been studied for various pharmacological actions such as anti-microbial [11], anthelmintic [12], anti-pyretic [13], anti-inflammatory [14], anti-oxidants [15], insecticidal [16],

immunomodulatory [17], anti-diarrheal [18], etc. due to the existence of various phytoconstituents. The stem bark and flowers were evaluated for the total tannin content and anti-oxidant activity [19]. Roots are used to treat rheumatism, cough and hiccup by Philippines [3, 20, 21]. As the whole plant is used as cough cure [10]; in the current work, we have looked into the phytoconstituents and anti-asthma activity of the *Quisqualis indica* leaves. The leaf petroleum ether extract (LPE) and leaf methanolic extract (LME) of *Quisqualis indica* were screened for phytochemicals by High Resolution Liquid Chromatography Mass Spectroscopy /Mass Spectroscopy (HRLCMS/MS) and anti-asthma activity. In the case of *Quisqualis indica* extract, which is high in flavonoids and phenolic compounds, reduces inflammation [14] and act as an immunomodulatory. [17]

Methods

Collection and preparation of plant material

The fresh leaves of *Quisqualis indica* Linn. plant were collected from the residential region in the Indian state of Maharashtra near Nashik. The plant was verified by the India Botanical Survey, which included Pune and Maharashtra [22, 23]. The allotted authentication No. was BSI/WRC/IDEN.CER/2016/403 (A). The pulverized and sieved dried leaf powder was processed. The petroleum ether (60–80 °C) and methanol solvents were used to extract the phytochemicals such as steroids, flavonoids, tannins; alkaloids, etc. The petroleum ether (60–80 °C) and methanol solvents were used in a continuous hot percolation process (Soxhlet extraction) to extract the coarse powder successively for 48 h. A rotating vacuum evaporator (Evator) was used to concentrate the liquid extracts to produce a semisolid extract [24, 25].

Animals

The healthy adult Wistar albino mice (20–25 g) of either sex were housed in polypropylene cages, under 12 h light: 12 h dark cycle and temperature 22 ± 2 °C and humidity 55 ± 5% maintained in the animal house. The animals had free access to food and water. All the animals were deprived of food but not of water 4 h before the experiment [26]. The Institutional Animal Ethical Committee of the institute (Registration No. 121/1999/CPCSEA) has approved all the protocols of the study (Registration No. IAEC/Jan 2020/09).

Acute oral toxicity study

The acute oral toxicity study OECD guideline (2001) [26, 27] was followed to carry out acute toxicity study for the extracts of *Quisqualis indica* plant.

Mast cell degranulation

There were six groups of mice in total, with six mice in each group. A three-day treatment for drugs program has been followed properly. Group I Control groupwas given the treatment with 1% tween 80 solutions (5 ml/kg, i.p.); Group II received standard drug Sodium chromoglycate (50 mg/kg, i.p) and all test groups Group III to Group VI received LPE and LME at doses of 200 and 400 mg/kg. On the fourth day, 10 mL/kg of 0.9% saline solution was gently massaged into the peritoneal cavity of each mouse before being injected. Five minutes later, the peritoneal fluid was collected. The peritoneal fluid was then put into a test tube containing 7–10 mL of RPMI-1640 buffer medium (pH 7.2–7.3), which is made up of L-glutamine and 25 mM HEPES buffer but not sodium bicarbonate. At 400–500 rpm, this solution was then centrifuged. Centrifugation was used to rinse the mast cells pellets twice with RPMI-1640 buffer media, and the supernatant was rejected. Egg albumin was used to challenge the cell suspension produced from both the treated and control groups of mice, which was then incubated at 37 °C for 10 min.After being stained with 1% toluidine blue, the cells were examined under a microscope. Mast cells that had degranulated were seen as rupture cells rather than whole. In total of 100 cells from various visual regions were counted, and the percentage of protection against degranulation was calculated [28, 29].

$$\%Protectionmastcell = [1 - (T/C)]x100$$

where, T- No. of degranulated cells of test
C-No. of degranulated cells of control

Milk induced eosinophilia and leukocytosis

There were six groups of mice, six animals in every group. Blood samples (0.5 ml) were collected from the retro-orbital plexus. Group I Control group received vehicle, tween 80 (1%) solution (5 ml/kg, i.p.); Group II received Standard drug Dexamethasone (50 mg/kg, i.p) and test groups Group III to Group VI received LPE and LME at doses 200 and 400 mg/kg. Amul's Fresh milk was procured from the local market. All animals were treated with an injection of freshly cooked and chilled milk (4 mL/kg, s.c.) for 30 min following treatments. Total leukocyte and eosinophil count were carried out in each group before drug administration and 24 h after the milk injection. Difference in total leucocytes count before and after 24 h of drug administration was calculated [30, 31].

Statistical analysis

All the results of various studies were expressed as mean ± Standard Error of Mean. Data was analyzed

using a one-way ANOVA, which was followed by Dunnet's Multiple Comparison Test. $P < 0.05$ was considered statistically significant. The graphs were calculated with the GraphPad Prism 5.

HRLCMS/MS profiling

The phytochemicals of the bioactive extract (LME) were analysed by HRLCMS/MS method. High-resolution liquid chromatography combined with the Q-Exactive Plus Mass Spectrometer TOF/Q-TOF mass spectrometer with ion source dual AJS electrospray ionization (ESI) was used [32]. The plant extract (50 mg) was dissolved in 1 mL of water: acetonitrile (1:1) solvent mixture, ultrasonically processed for 10 min, and then centrifuged at 10,000 rpm for 10 min. The ZORBX Eclipse Plus C18, narrow bore 2.1 150 mm with 5 microns, was used for the LC/ESI-QTOF-MS/MS analysis. An amount of 5µL was delivered in both positive as well as negative mode. The Mass Spectra scan range was in 120 to 1200, with 1.00 scans rate spectra/second and 1.00 as MS/MS scan rate spectra/second. The gradient elution procedure was done by changing the proportion of water and acetonitrile from 95 to 5% within 30 min, with flow rate of 0.3 mL/min as a constant flow rate. Then, this section was linked to the TOF/Q-TOF Mass Spectrometer for MS/MS fragmentation spectra. Phytochemicals were recognized by comparing their m/z and MS/MS transitions with those documented in reference databases. Further, the molecular formula, retention time, and adduct formula were detected.

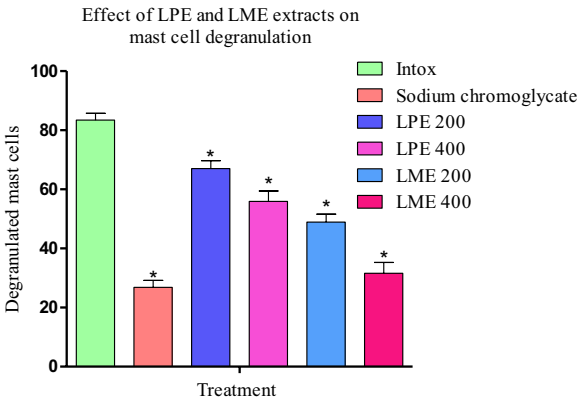


Fig. 1 Effect of Quisqualis indica leaf extracts on egg albumin induced degranulation of mast cell

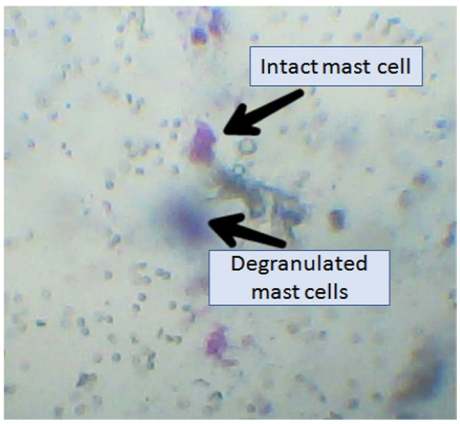


Fig. 2 Mast cell granulated and degranulated

Results

Acute oral toxicity study

Oral administration of plant extracts shows no significant body weight variation, neither any sign of toxicity nor mortality of mice at the dose of 2000 mg/kg, body weight.

Mast cell degranulation

In the pathogenesis of allergic asthma, mast cells also play a crucial role. Inhaled antigens enter the lower respiratory tract and produce localised mast cell degranulation and inflammation that trigger an inflammatory response in the airways. These circumstances cause edema, fluid build up, and increased vascular permeability, which can block the airways. Asthma-related airway obstruction can result from bronchial constriction, which can happen as a result of smooth muscle contraction [33]. Novel medications or treatments that help lessen asthma symptoms by lowering the production of these inflammatory mediators can be found by researching the inhibition of mast cell degranulation. In the present study, the effect of LPE and LME at doses of 200 and 400 mg/kg, body weight was examined on mast cell degranulation. The control group showed (83.4 ± 0.34) degranulation of mast cells while groups pre-treated with extracts and disodium chromoglycate significantly protect degranulation of mast cells. [34, 35] LME at dose (400 mg/kg) showed (31.6 ± 3.67) and disodium chromoglycate (26.86 ± 2.34) protection against degranulation as shown in Figs. 1 and 2.

Values are in Mean ± SEM, $^{*}P < 0.05$ when compared against control, $n = 6$. One Way ANOVA was used to analyze all the data, and then Dunnett's test was performed. The graph was calculated by using PRISM 5 Software.

Milk induced eosinophilia and leukocytosis

Airway hyperresponsiveness (AHR), reversible airflow restriction, and airway inflammation are all symptoms of bronchial asthma, a chronic condition. Eosinophilic asthma and non-eosinophilic asthma are two types of asthma's pathophysiological mechanisms. According to recent studies, eosinophils are crucial to the emergence of asthma exacerbations. Immune-modulatory

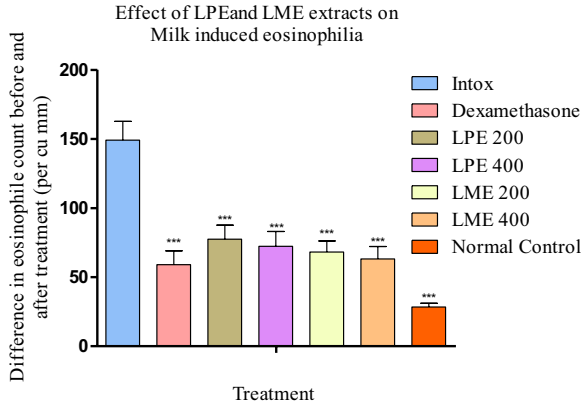


Fig. 3 Effect of Quisqualis indica leaf extracts on Milk induced eosinophilia

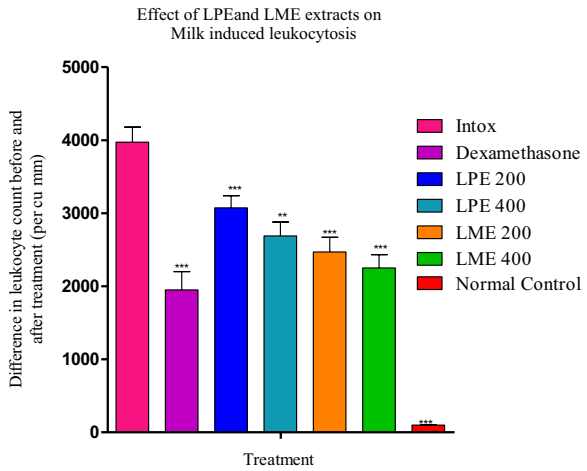


Fig. 4 Effect of Quisqualis indica leaf extracts on milk induced leukocytosis

reactions brought on by a high blood eosinophil count include airway inflammation, hyperresponsiveness, epithelial lining damage, and increased mucus secretion, Eosinophilic inflammation affects nearly fifty percent of asthma sufferers. Studies have proven that eosinophilia has been associated with higher disease severity, exacerbation frequency, and symptom burden, as well as decreased lung functions [36]. Therefore, eosinophilic inflammation must be suppressed and eosinophilic and non-eosinophilic asthma must be distinguished in order to treat or avoid asthma aggravation [37]. The maximum increase in difference of eosinophil (578.00 ± 11.10) and leucocytes (11,266.16 ± 149.63) counts was found in the control group which has been treated with milk (4 mL/kg, s.c.) before 24 h *Quisqualis indica* extracts at doses of 200 and 400 mg/kg significantly inhibited milk-induced eosinophilia and leucocytosis in a manner dependent on dose. Like Dexamethasone [38], the LME (400 mg/kg) exhibits substantial inhibition as shown Figs. 3 and 4.

Values are in Mean ± SEM, $^{***}P < 0.05$ when compared against control, $n = 6$. One Way ANOVA was used to analyze all the data, and then Dunnett's test was performed. The graph was calculated by using PRISM 5 Software.

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LCMS/MS study of the bioactive extract

The LC–MS chromatogram of the methanolic extract of *Quisqualis indica* is shown in Figs. 5 and 6, and the important identified compounds are given in Tables 1 And 2.

Discussion

A persistent inflammatory illness of the airways is allergic asthma. Leukocyte infiltration into the lung and airway is the primary characteristic of asthma [39]. In the current study, mice with milk-induced eosinophilia and leukocytosis were used to test the anti-asthmatic activity of LPE and LME at doses of 200 and 400 mg/kg. According to reports, giving milk subcutaneously causes a noticeable rise in the number of leukocytes and eosinophils 24 h later. Inflammatory mediators such as cytokines, histamine, and major basic proteins are released by leucocytes during asthmatic inflammation, promoting the continued inflammation. A peripheral eosinophil count that has abnormally increased to over 4% of the total leukocyte count is referred to as eosinophilia. The eosinophil count rises in asthmatic patients [40, 41].

While mice treated with various doses of plant extracts show a decrease in the difference in leukocyte and eosinophil counts, mice treated with 1% Tween-80 in the control group exhibit an increase in these two cell types. *Quisqualis indica* leaf extracts may be helpful in allergy conditions because adaptogenic and type I hypersensitivity mediate the decrease in leucocytes and eosinophils.

Mast cells degranulate in response to immunological stimuli where antigen antibody responses are prevalent. In a dose-dependent way, *Quisqualis indica* leaf extracts at doses of 200 and 400 mg/kg effectively prevent egg albumin-induced mast cell degranulation. At 400 mg/kg, LPE and LME protect mast cells similarly to disodium chromoglycate. This demonstrates the effectiveness of *Quisqualis indica* leaf extracts in type I hypersensitivity reactions and in mast cell stabilization. The anaphylactic allergic reaction, which can be triggered by a variety of triggers, is a potentially fatal reaction that releases mediators like histamine and pro-inflammatory cytokines.

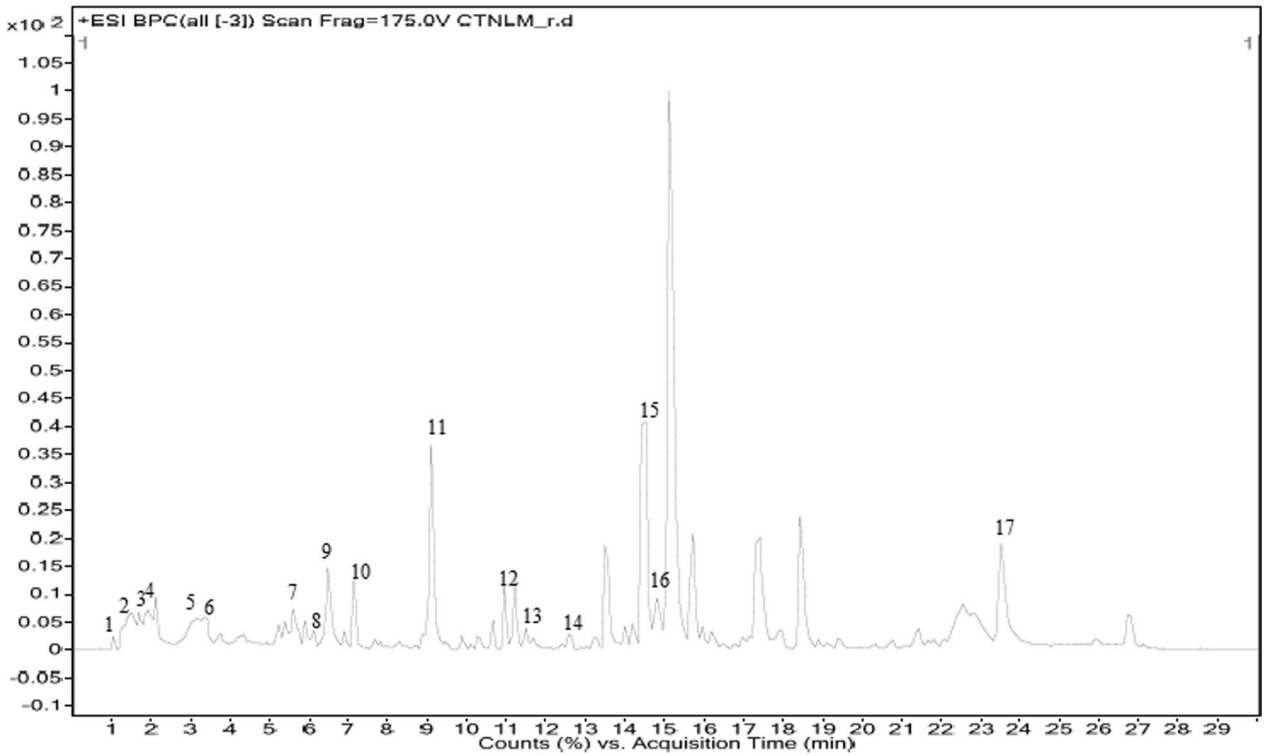

Fig. 5 Chromatogram of LME of *Quisqualis indica* positive ESI

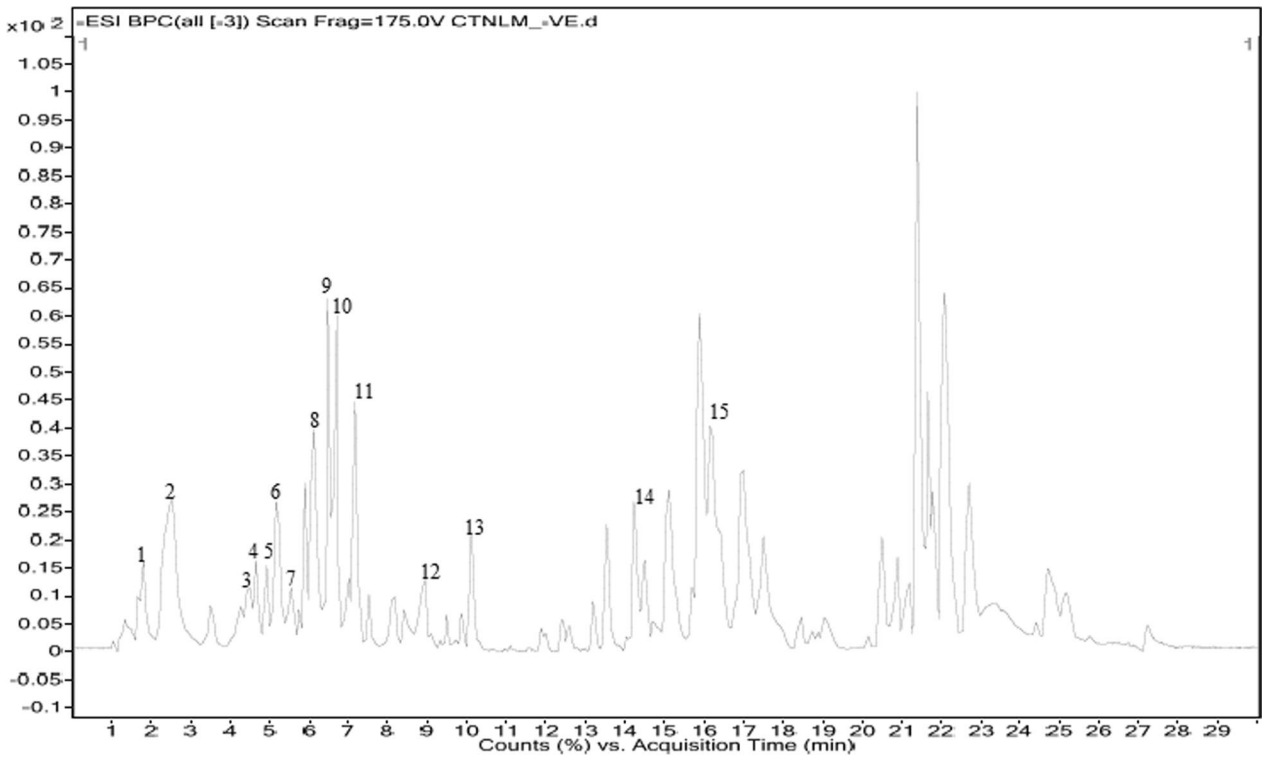

Fig. 6 Chromatogram of LME of *Quisqualis indica* negative ESI

Table 1 Important compounds identified in LME extract of *Quisqualis indica* by HRLCMS/MS positive ESI

Peak No	Retention time	Abundance	Name of compound	Molecular formula
	1.289	150,556	L-Proline	C5H9NO2
	1.337	45,242	Retronecine	C8H13NO2
	1.873	237,178	Fenapanil	C16H19N3
	1.926	200,358	Neotussilagine	C10H17NO3
	3.149	325,229	Ketotifen	C19H19NOS
	3.439	348,266	N(alpha)-t-Butoxycarbonyl-L-leucine	C11H21NO4
	5.704	136,079	Crotanecine	C8H13NO3
	6.222	121,724	6-C-Galactosylluteolin	C21H20O11
	6.515	379,580	Apigenin7-glucoside	C21H20O10
	7.138	299,350	Maritimetin	C15H10O6
	9.335	80,034	N1,N5,N10- Tricoumaroylspermidine	C34H37N3O6
	11.25	122,878	Phenmedipham	C16H16N2O4
	11.561	83,930	Sulfadimidine	C12H14N4O2S
	12.666	99,466	Schleicherastatin 6	C28H46O3
	14.802	267,218	23-Acetoxysoladulcidine	C29H47NO4
	14.887	190,078	Citronellyl hexanoate	C16H30O2
	23.236	197,160	Goyaglycoside c	C38H62O9

Table 2 Important compounds identified in LME extract of *Quisqualis indica* by HRLCMS/MS negative ESI

Peak No	Retention time	Abundance	Name of compound	Molecular formula
	1.734	129,716	1-O-Caffeoyl-(b-D-glucose 6-O-sulfate)	C15H18O12S
	2.59	206,438	Gallicacid	C7H6O5
	4.445	69,208	Chorismicacid	C10H10O6
	4.839	46,662	Kurigalin	C27H24O18
	4.893	3176.86	PunicacorteinB	C27H22O18
	5.189	14,789	Salicylicacid	C7H6O3
	5.864	297,109	Quercetin3-(2-galloyl glucoside)	C28H24O16
	6.503	1,238,967	Genistein8-C-glucoside	C21H20O10
	6.653	10,369	Myricitrin	C21H20O12
	6.94	297,109	Clocortolonepivalate	C27H36ClFO5
	7.167	152,689	Quercitrin	C21H20O11
	8.966	39,705	Kaempferol	C15H10O6
	10.103	45,242	Luteolin	C15H10O6
	14.291	–	Geranylfarnesyl diphosphate	C25H44O7P2
	16.371	13,987	StigmatellinY	C29H40O6

The methanolic extract was subjected to a phytochemical analysis using the HRLCMS/MS technique, which revealed the presence of a number of phytocompounds including apigenin 7-glucoside, 3-Oxo-12, 18-ursadien-28-oic acid, 1-O-Caffeoyl-(b-D-glucose 6-O-sulfate), gallic acid, kurigalin, punicacortein B, etc. Gallic acid has shown a good amount of abundance in LME extract and acts by inhibiting mast cell activation, preventing the release of histamine, and the production of pro-inflammatory cytokines [42]. The highly galloylated compounds inhibits secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in a concentration-dependent manner, acting on the transcriptional activity of NF-κB [43]. According to the pharmacological effects of flavonoids like kaempferol, quercetin, and rutin, they may be able to treat allergic inflammatory disorders by inhibiting mast

cell activation [44]. Apigenin has been found to be effective in allergic asthma through the decreased activation of epithelial cells, T cells, and eosinophils [45]. As per HRLCMS data of LME extract the flavonoids like kaempferol, quercetin, apigenin, and luteolin and few types of tannin like gallic acid and punicacortein B are present in a notable amount. As a result, *Quisqualis indica*'s leaf methanolic extract has shown significant mast cell degranulation and Milk-induced eosinophilia and leukocytosis action. Hence, *Quisqualis indica* leaves may be helpful in allergic conditions like asthma.

Conclusion

The plant extract is found to comprise phytochemicals such as apigenin 7-glucoside, 3-Oxo-12, 18-ursadien-28-oic acid, 1-O-Caffeoyl-(b-D-glucose 6-O-sulfate), gallic acid, kurigalin, punicacortein B, apigenin, kaempferol, quercetin, rutin, nicotinic acid methylbetaine (trigonelline), L-proline, L-asparagine, potassium quisqualate, etc. Thus, this plant is a plentiful source of phytochemicals with therapeutic value, and the findings of this study offer some scientific support for the use of the plant in traditional medicine for anthelmintic, anti-emetic, analgesic, antiulcer, and anti-diarrheal purposes. The results of the current investigation showed that milk-induced leucocytosis and eosinophilia reduced significantly by *Quisqualis indica* leaf extracts at 400 mg/kg dose. In anaphylactic reactions, extracts suppress the release of histamine and stabilize antigen-induced mast cells. They also have anti-allergic properties. As a result of its anti-allergic and mast cell-stabilizing properties, which might be due to the presence of flavonoids, tannins, and triterpenoids, *Quisqualis indica* leaf extracts are beneficial in treating asthma.

Abbreviations

LPE	Leaf petroleum ether extract
LME	Leaf methanolic extract
OECD	The Organization for Economic Cooperation and Development
HRLMS/MS	High Resolution Liquid Chromatography Mass Spectroscopy / Mass Spectroscopy
AJS	Jet Stream Technology Ion Source
ESI	Electrospray ionization
TOF/Q-TOF	Tandem time-of-flight /quadrupole Tandem time-of-flight
RPMI-1640	Roswell Park Memorrial Institute
ANOVA	Analysis of Variance

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Author contributions

CTN carried out the sample collection, conceptualisation, extraction and anti-asthma activity, HRLCMS/MS analysis, results interpretation and write-up. The other author read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of MVP's College of Pharmacy, Nashik, Maharashtra, India (Registration No. 121/1999/CPCSEA) constituted under Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Annexure 1). The animal ethical committee of the institute has approved all the protocols of the study (Registration No. IAEC/Jan 2020/09).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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