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Research Paper / Araştırma Makalesi

Evaluation of Anti-Allergic Property of Mulmina™ Mango Juice in *In Vivo* Models

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ABSTRACT

Mulmina™ mango juice is the brand name of the formulation containing *Mangifera indica* L., *Centella asiatica*, *Curcuma longa,* essential vitamins and minerals. Mulmina™ is natural immune booster and stress reliever. The present study is to investigate the effect of Mulmina™ mango juice for its anti-allergic property by *in vivo* models like: Compound 48/80 induced mast cell degranulation in rat mesentery, rat peritoneal fluid, milk induced leucocytosis and eosinophilia in mice and systemic anaphylaxis in mice. Mulmina™ mango juice exhibited potential anti-allergic property with marked reduction in number of degranulated cells, reduction in antigen (milk) induced immunological reaction by lowering leucocytes and eosinophil count and showed protection against histamine induced anaphylactic shock. These results constitute the first report of the anti-allergic properties of Mulmina™ mango juice on allergic models, as well as suggesting that this natural fruit juice could be successfully used in the allergic conditions.

Keywords: Mulmina mango juice, Allergy, Leucocytes, Eosinophil, Anaphylaxis

Mulmina™ Mango Suyunun Anti-Alerjik Özelliğinin *In Vivo* Modellerde Değerlendirilmesi

ÖZ

Mulmina™ mango suyu, *Mangifera indica* L., *Centella asiatica*, *Curcuma longa*, temel vitaminler ve mineraller içeren formülasyonun marka adıdır. Mulmina™ doğal bağışıklık güçlendirici ve stres gidericidir. Bu çalışmada Mulmina™ mango suyunun anti-alerjik özelliği için etkisi *in vivo* modellerle araştırmaktadır: Bileşik 48/80, fare mezenterinde mast hücre degranülasyonunu, fare periton sıvısını, farelerde süt kaynaklı lökositoz ve eozinofiliyi ve sistemik anafilaksiyi indüklemiştir. Mulmina™ mango suyu, degranüle hücre sayısında belirgin azalmaya neden olmuş, lökosit ve eozinofil sayısını düşürerek antijen (süt) kaynaklı immünolojik reaksiyonda azalma ile potansiyel anti-alerjik özellik sergilemiş ve histamin kaynaklı anafilaktik şoka karşı koruma göstermiştir. Bulgular, Mulmina™ mango suyunun alerjik modeller üzerindeki anti-alerjik özelliklerini bildiren ilk çalışmadır ve bu doğal meyve suyunun alerjik koşullarda başarıyla kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Mulmina mango suyu, Alerji, Lökositler, Eozinofil, Anafilaksi

INTRODUCTION

The prevalence of allergic diseases in Western countries has risen substantially over the last few decades [1]. Allergy may be defined as the potential for development of immunologically mediated reactions to allergens, which in 80% of the allergy-based clinical diseases in man [2]. Exposure to an antigen sets off an immune-mediated cascade of inflammatory events. First, the allergen is broken down into smaller peptides and exposed to T cells by antigen-presenting cells. The T cells produce cytokines such as interleukin 4 (IL-4) that induce B cells to produce antigen-specific IgE, which binds to high affinity FceRI receptors on basophils and/or mast cells [3]. On a second encounter with the same allergen, the allergen cross-links the IgE bound to FceRI receptors, activating them and causing the release of inflammatory mediators such as histamine, prostaglandins, and leukotriene [4]. Preformed mediators, such as histamine, neutral proteases and other enzymes, and chemotactic factors, are present in granules and released by fusion of the granule membranes with the cell membrane. Other substances, such as cytokines, and lipid mediators, such as prostaglandins and cysteinyl leukotrienes (LTC4, LTD4 and LTE4) are newly synthesized and secreted following cross-linking. Current treatment of allergic symptoms consists of antihistamines, leukotriene receptor antagonists [5-9]. mast-cell stabilizers [10-11], and corticosteroids [12]. Some of the above treatments cause severe adverse effects [11-14].

In recent years, there has been an increasing interest on natural products that possess potential health benefits, particularly those derived from herbal sources. Among these, Mulmina mango herbal juice, manufactured by Jagadale Industries Pvt. Ltd., stands out as a unique product due to its formulation and claimed health benefits. Marketed as the world's first aseptic Tetra Pak product under the label of Vedic nutrition, Mulmina™ mango herbal juice is promoted as a natural immune booster. The primary ingredients of Mulmina mango herbal juice include *Mangifera indica*, *Centella asiatica* extract, *Curcuma longa*, and other nutritional components, including β-carotene, various B vitamins (B1, B2, B3, B5, B6, B9), Vitamin C, Vitamin E, Zinc, Iron, and selenium. These nutrients play crucial roles in supporting immune function, antioxidant defence, and overall health.

Mangifera indica L. fruit pulp (Fam. Anacardiaceae) commonly known in India as mango (aam). Mango possess extensive array of nutrients and beneficial phytochemicals. The tropical fruit is rich in essential vitamins such as vitamins (A, C and E), minerals (potassium, magnesium, selenium), polyphenols (magniferin, quercetin and kaempferol). Studies suggest that due to the presence of polyphenols and flavonoids in mangoes may help to modulate allergic response by reducing the release of histamine and other inflammatory mediators [15]. The pharmacological activities of mongo: antiallergic, antifungal, antitumor, antiamoebic, spsmolytic, anti-inflammatory, analgesic, antioxidant and immunomodulatory properties [16-19].

Centella asiatica Linn, belonging to the Apiaceae family and commonly known as Madukaparni or Gotu Kola, is celebrated for its extensive therapeutic properties that have been recognized in both traditional and modern medicine. C. asiatica is recognized for its antiallergic properties, attributed to its rich phytochemicals composition and pharmacological actions [20]. *Centella asiatica* has different therapeutic properties like wound healing, anticancer, anti-allergic, anti-inflammatory, antileprotic antinociceptive and antidiabetic. Important active constituent's presents in *Centella asiatica* are glycoside, triterpenoid saponins, including asiaticoside, centelloside, madecassoside and asiatic acid, rhanmanose. In addition, *Centella* contains other components, including volatile oils, flavonoids, tannins, phytosterols, amino acids and sugars [21-24].

Curcuma longa Linn, commonly known as turmeric and belongs to family Zingeberaceae has traditionally been used to treat pain, fever, allergic and inflammatory diseases such as bronchitis, dermatitis and arthritis. Turmeric has been also studied expansively for its pharmacological activities such as antioxidant, anti-inflammatory, anti-cancer, anti-microbial, and neuroprotective effects [25-29]. Curcumin, a main ingredient derived from turmeric, has been also claimed to be an antioxidant and anti-inflammatory agent [30].

The present study aims to evaluate the anti-allergic properties of Mulmina™ mango herbal juice (Figure 1), building upon the rich tradition of using natural remedies to promote health and well-being. By exploring the potential benefits of this herbal formulation, this research seeks to contribute to the growing body of knowledge on natural products in modern healthcare, highlighting their role as complementary or alternative therapies to conventional medicine.

Figure 1. Mulmina™ mango juice

MATERIALS and METHODS

Chemicals and Reagents

Compound 48/80, Histamine, ovalbumin, Thiobarbituric acid (TBA) with Malondialdehyde (MDA) Sulphanilamide and N-1-napthylethylenediamine dihydrochloride (NED) reduced glutathione (GSH), 5,5-dithiobis-2-nitrobenzoic acid, thiobarbituric acid and trichloroacetic acid were purchased from Hi-media Laboratories Pvt. Ltd, Mumbai, India. All the other chemicals used were of analytical grade.

Animals

Adult albino Wistar rats (180-220 gm), albino mice (18 - 20 gm) were used for the present study. The animals were housed in animal house of Sree Siddaganga College of Pharmacy, Tumkur, Karnataka, India. The animals were maintained under controlled condition of temperature (23±2°C), humidity (50±5%) and 12 h light-dark cycle. The animals were acclimatized for seven days before the study. The animals were randomly divided into groups and individually housed in a sanitized polypropylene cage. Animals were habitude to laboratory conditions for 48 hours to minimize if any non-specific stress. The animals were free assessed to standard pellets as a basal diet and water *ad libitum.* The experimental protocol was approved by the institutional animal ethical committee and conducted according to CPCSEA guidelines, Govt. of India.

Mulmina^{TM} Mango Juice Preparation for Studies

Mulmina^{TM} mango juice recommended for human two 400 mL per day as a natural antioxidant and immune booster. The animal dose was calculated by using USFDA dose conversion guidelines ie Animal Effective dose (AED) mg/kg =Human Effective Dose (mg/kg) X Dose conversion factor. Accordingly, Rat dose conversion factor 6.2 and Mouse conversion factor 12.3 were used for the dose calculation for rats and mouse. Rat dose used was 42 mL/kg as high dose and 21 mL/kg as low dose similarly for mouse high dose was 82 mL/kg and low dose of 41 mg/kg body weight used for studies.

Anti-Allergic Screening of Mulmina Mango Juice

Compound 48/80 Induced Mast Cell Degranulation in Rat Mesentery

Male Wistar rats (180-200 g) were selected and acclimatized for 7 days [31]. Randomized into six groups, each containing eight animals. Sensitization with compound 48/80 (1 mg/kg, i.p) on first day after 2 h of treatment except group I and II. Each group received respective treatment up to 7 days. The animals were sacrificed under overdose of anaesthesia. Mesentery was collected and challenged with Compound 48/80. Numbers of intact and degranulated cells were observed and percentage protection was calculated.

Compound 48/80 Induced Mast Cell Degranulation in Rat Peritoneal Fluid

The Male Wistar rats (180-200 gm) acclimatized for 7 days and divided into six groups, each containing eight animals [32]. Sensitization with Compound 48/80 (1 mg/kg, i.p) on first day after 2 h of treatment except group I and II. Each group received respective treatment up to 7 days. On 7th day after 2 hours of respective treatment, 10 mL of normal saline was injected into rats through peritoneal cavity. After a gentle massage of peritoneal region for a period of 5 minutes, peritoneal fluid was collected. 1 mLof collected peritoneal fluid was mixed in a 2 mL Eppendorf tubes containing 1mL of RPMI-1640 (Roswell Park Memorial Institute-1640) at pH 7.2-7.4. Then, the tube containing peritoneal fluid with RPMI-1640 media was centrifuged twice at low speed (400-800 rpm) for 10 min. Further, discard the supernatant and the pellets containing mast cells re-suspended in 2 mL RPMI-1640 media. The mast cells suspension placed on fresh and clean glass slide. Smear was prepared on a glass slide, and challenged with compound 48/80 (5µg/ mL) and air-dried. Then, the slides stained with 0.1% toluidine blue in 4% v/v aqueous formalin solution for 10 min. The stained cells were then immersed in xylene for 5-10 min and finally rinsed 2 or 3 times with acetone and was observed under microscope at high power. Total of 100 cells from different regions of different visible areas was counted on prepared slide. Then record the number of intact and degranulated mast cells and percentage protection was calculated.

Milk Induced Leucocytosis and Eosinophilia in Mice

Blood samples were collected from each mouse via retro-orbital plexus before drug administration and were collected in an EDTA coated tubes for analysis [33]. (Leucocytosis and eosinophils). After 45 minutes of the respective treatments to the same grouped mice received boiled and cooled cow milk through subcutaneous route except group I and II. After 24 h blood were withdrawn from retro-orbital plexus and were collected in an EDTA coated tubes for count from Group I to VI.

a. Total leukocyte: Samples were diluted with WBC diluting fluid (1:1) using WBC pipette. Diluted blood in a pipette were shaken and kept aside for 5 min and total leucocyte count were determined by using Neubauer's chamber.

b. Eosinophils count: Smear on plane slide was prepared using collected blood samples. Leishman's stain was used for staining the smears. This caused eosinophils to show up as orange-red granules. Then the eosinophil cells were counted under light microscope at 45X and tabulated.

Effect of Mulmina Mango Juice on 48/80-Induced Systemic Anaphylaxis

Swiss albino mice (20-25) g of either sex were selected and randomly divided into four groups of ten animals each [34-36]. After the administration of the anaphylactic

shock by compound 48/80 (8 mg/kg, i.p.) the mice were observed for mortality. Over the period of observation throughout 1 h, mortality of animals from all groups were noted. The percentage of mortality were calculated using the formula

$$\text{Percentage mortality} = \frac{\text{The number of dead mice}}{\text{Total number of experimental mice}} \times 100$$

Statistical Analysis

All experimental data was expressed as Mean ± S.E.M (n = 6), Statistical evaluation was done by One-way ANOVA followed by Tukey's post hoc test. a *p< 0.001* was considered significant.

RESULTS

In the model of compound 48/80 induced mast cell degranulation in rat mesentery, the compound 48/80 alone used to sensitize the rats. The isolated mesentery showed extensive degranulation of mast cells and found significantly ($p<0.001$) high number of degranulated mast cells 75.5±3.87 than the normal control group (10.3±0.65) (Table 1 & Figure 2). It was noteworthy from the that treatment with Mulmina™ mango juice (21 mL/kg & 42 mL/kg) exhibited significant reduction ($p<0.001$ & $p<0.001$) in number of degranulated cells (27.4±1.17 & 15.1±0.54) and the percentage protection was found to be (63.70% & 80.00%) when compare to compound 48/80 alone group. Moreover, rats treated with the standard drug ketotifen fumarate (1mg/kg) showed marked reduction ($p<0.001$) in number of degranulated cells (18.8±0.64) with 75.09% protection in compare to compound 48/80 alone group. Treatment of Mulmina™ mango juice to chemically induced mast cell degranulation in rat mesentery exhibited comparable protection as that of standard ketotifen fumarate (1mg/kg).

Table 1. Effect of Mulmina™ mango juice in 48/80-induced mast cell degranulation in rat mesentery

Groups	Treatment*	Percentage (%) Intact mast cell	Percentage (%) degranulated mast cell	Percentage (%) protection
I	Normal control	89.72±0.65	10.3±0.65	NA
II	Mulmina™ alone	89.04±1.14	11.0±1.14	NA
III	Inducer control (Compound 48/80)	24.49±3.86$^{###}$	75.5±3.87$^{###}$	NA
IV	Mulmina™ (21 mL/kg p.o.)	72.64±1.17***	27.4±1.17***	63.70
V	Mulmina™ (42 mL/kg p.o.)	84.86±0.54***	15.1±0.54***	80.00
VI	Standard (Ketotifen 1 mg/ kg)	81.19±0.64***	18.8±0.64***	75.09

*Each value represent the Mean±S.E.M (n=6), $^{###}P<0.001$ compared to normal control; $^{***}P<0.001$ compared to Compound 48/80 group. NA= Not applicable. Statistical evaluation was done by Tukey's posthoc test.

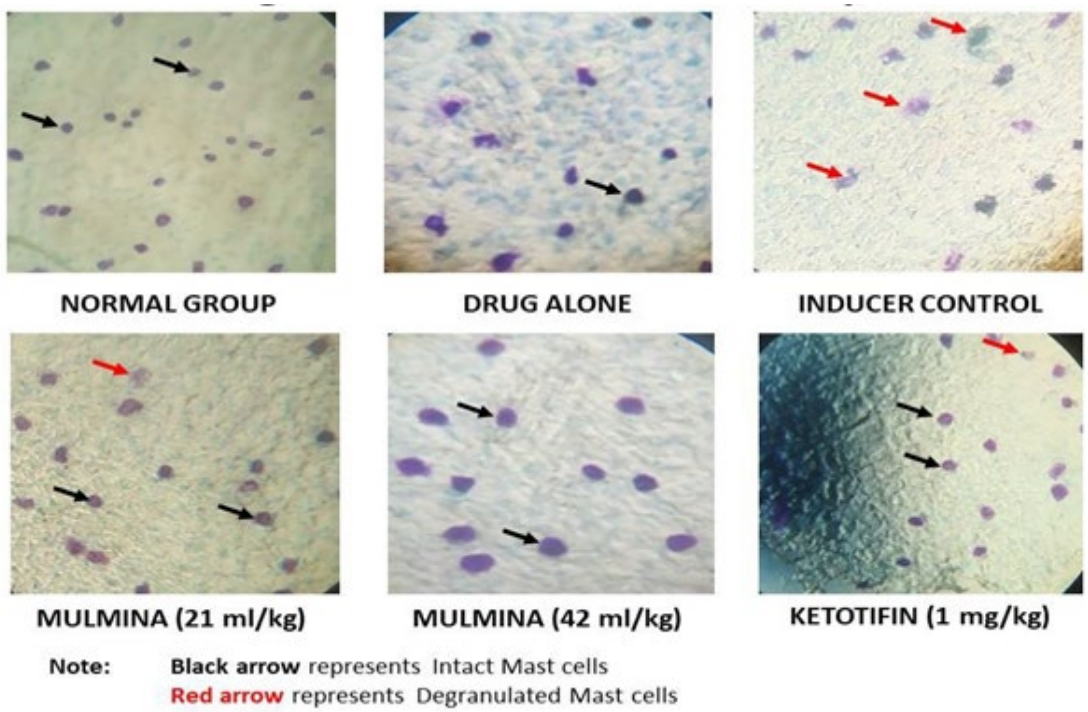

Figure 2. Effect of Mulmina™ mango juice in 48/80-induced mast cell degranulation in rat mesentery

In the experiment model of compound 48/80 induced mast cell degranulation in rat peritoneal fluid, the experimental rats were sensitized and challenged with compound 48/80. The peritoneal fluid of inducer control groups rats showed significant ($p<0.001$) increase in degranulation of mast cells (87.54±0.46) when compared to normal control group (15.34±0.85) (Table 2 & Figure 3). Treatment with Mulmina^{TM} mango juice (21 ml/kg and 42 mL/kg) showed significant ($p<0.001$) reduction in number of degranulated cells (23.31±0.88 & 13.53±1.03 respectively) when compare to the compound 48/80 alone group. Both the treatment doses showed 73.37% and 84.54% protection against mast cell degranulation challenged with compound 48/80. Tallying with standard drug Ketotifen fumarate (1mg/Kg) which showed significant ($p<0.001$) decreased number of degranulated mast cells and protection was found to be 77.02% when compared to compound 48/80 group. In comparison with normal rats treated with the higher dose of Mulmina^{TM} mango juice alone did not caused degranulation suggesting the safety of tested formulation. The higher dose of Mulmina^{TM} mango juice showed slightly higher protection in comparison with tested standard compound.

Table 2. Effect of Mulmina^{TM} mango juice in compound 48/80 induced mast cell degranulation in rat peritoneal fluid.

Treatment*	Percentage (%) Intact mast cell	Percentage (%) degranulated mast cell	Percentage (%) protection
Normal control	82.9±1.86	15.34±0.85	NA
Mulmina^{TM} alone	82.2±0.51	11.86±0.74	NA
Inducer control (Compound 48/80)	12.5±0.46$^{###}$	87.54±0.46$^{###}$	NA
Mulmina^{TM} (21 mL/kg p.o.)	76.70±0.88***	23.31±0.88***	73.37
Mulmina^{TM} (42 mL/kg p.o.)	86.5±1.03***	13.53±1.03***	84.54
Standard (ketotifen 1 mg/ kg)	79.9±1.17***	20.11±1.17***	77.02

*Each value represent the Mean±S.E.M (n=6), $^{###}p<0.001$ compared to normal control; $^{***}p<0.001$ compared to Compound 48/80 group. NA= Not applicable. Statistical evaluation was done by One-way ANOVA followed by Tukey's posthoc test.

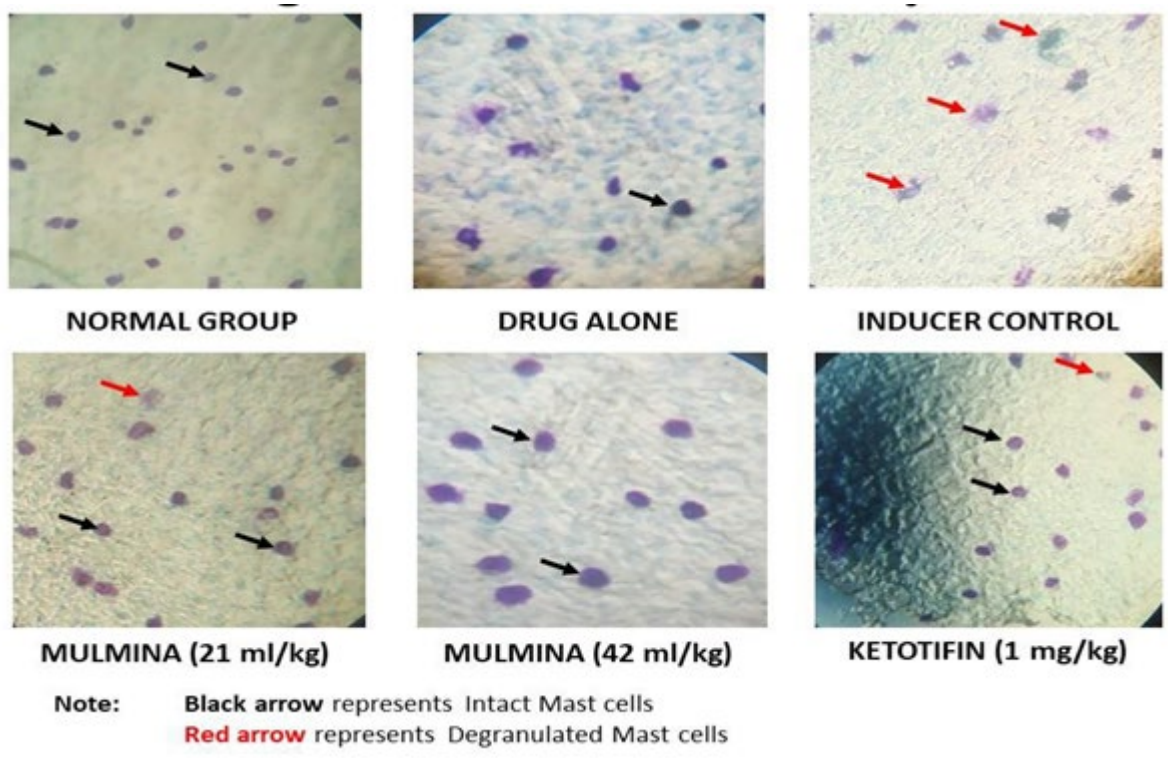

Figure 3. Effect of Mulmina^{TM} mango juice in compound 48/80 induced mast cell degranulation in rat peritoneal fluid.

In the milk, induced leucocytosis and eosinophilia in mice subcutaneous administration of milk (4 mL/kg) showed significant increase ($p< 0.001$) in the leucocytes and eosinophils count after 24 h compared to normal control group (Table 3). The group of mice pre-treated with Mulmina^{TM} mango juice (41 mL/kg and 82 mL/kg) exhibited significant decrease ($p<0.001$) in leucocytes and eosinophils levels. The reference standard of Dexamethasone (50 mg/kg) showed significant reduction ($p<0.01$; $p<0.001$) in leucocytes and eosinophils counts respectively and provide the validation of the model (In addition, Mulmina^{TM} mango juice alone treatment did not show serological responses (Total leukocyte & Eosinophil count**)** to antigen (milk).

Table 3. Effect of Mulmina™ mango juice on milk-induced leucocytosis and eosinophilia in mice

Treatment*	Difference in no. of Leucocytes (per mm^3)	Difference in no. of Eosinophils (%)
Normal control	133.3±103.7	0.305±0.378
MULMINA™ alone (41 mL/kg p.o.)	166.7±170.6	0.402±0.541
Inducer control (Milk 4mL /kg)	3390±198.5###	10.3±0.92###
MULMINA™ (41 mL/kg p.o.)	1195±314.2*** (64.75%)	2.69±0.308*** (75.87%)
MULMINA™ (82 mL/kg p.o.)	608.3±141.1*** (82.06%)	1.49±0.51*** (82.53%)
Dexamethasone (50 mg/kg)	800±238.7*** (76.40%)	1.17±0.209*** (88.64%)

*Each value represent the Mean±S.E.M (n=6), ###p< 0.001 compared to normal control; ***p< 0.001 compared to Milk alone group. Statistical evaluation was done by Tukey's posthoc test.

In the model of 48/80-induced systemic anaphylaxis, treatment with Mulmina™ mango juice and ketotifen fumarate 1 h prior to induction of compound 48/80 induces systemic anaphylaxis exhibits significant protection against anaphylactic shock and death. Oral administration of higher dose of Mulmina mango juice (82 mL/kg) showed 70% protection against mortality as compared to compound 48/80 alone group (100%). In addition, ketotifen fumarate showed 50% protection against mortality. Behavioural observations showed that treatments delayed the anaphylaxis. However, the lower dose of Mulmina™ mango juice (41 mL/kg) failed to show protective effect (Table 4).

Table 4. Effect of Mulmina™ mango juice on 48/80-induced systemic anaphylaxis

Groups	Number of death / 10 animals	% Mortality	% Protection
Compound 48/80 (8 mg/kg, i.p)	10	100%	0%
MULMINA™ (41mL/kg,p.o)+ Compound 48/80	10	100%	0%
MULMINA™ (82 mL/kg, p.o) + Compound 48/80	3	30%	70%
Ketotifen fumarate (1mg/kg, p.o) + Compound 48/80	5	50%	50%

DISCUSSION

In this study, the anti-allergic effects of Mulmina™ mango juice were investigated using animal models of allergy. Majority of diseases in man are allergy based, allergic reaction involves an immune-mediated cascade of allergic events due to exposed to antigens, the immune modulatory T cells will release interleukins, which induce B cells to produce antigen-specific immunoglobulin E (IgE), which binds to high affinity FceRI receptors on basophils and mast cells, leading to their degranulation and subsequent release of inflammatory mediators such as histamine, prostaglandins, and leukotriene [37-38]. These mediators cause the symptoms associated with allergic reactions, including inflammation, itching, and bronchoconstriction. Mast cells, in particular, play a significant role in the pathophysiology of asthma and other allergic diseases. Upon activation of allergens and other stimuli, mast cells release a variety of cytokines that regulate IgE synthesis and contribute to the development of eosinophilic inflammation.

Mulmina mango juice contains a variety of bioactive phytochemicals, including amino acids (lysine, leucine, cysteine, methionine, valine, arginine, and phenylalanine), vitamins (A, B, C, E and K), phenolic compounds (Mangiferin, gallic acid, gallotannins, quercetin, ellagic acid, epicatechin, quercetin, etc.,) triterpenoids, saponins, and curcumin. These phytochemicals have been reported to possess immune modulating, antioxidant, and anti-inflammatory properties, which may be responsible for antiallergic effect of Mulmina™ mango juice [39-40].

Phenolic compounds present in Mulmina™ mango juice inhibit the release of histamine from mast cells and reduce the production of pro-inflammatory cytokines [41] and also stabilize mast cells by preventing them from degranulation and the release of histamine and other inflammatory mediators [42].

Mulmina™ mango juice contains vitamins, reduce the production of histamine, thereby alleviating allergic symptoms [43], inhibit the synthesis of prostaglandins and leukotrienes, which are key mediators of inflammation in allergic reactions [44].

Curcumin's anti-inflammatory properties help reduce the production of pro-inflammatory cytokines and chemokines involved in allergic responses [45]. It also scavenges free radicals and inhibits oxidative stress, which can exacerbate allergic reactions [46]. Presence of amino acids in Mulmina™ mango juice play important role in the synthesis of glutathione, a potent intracellular antioxidant that helps in protection of cells from oxidative stress and inflammation [47].

The anti-allergic effect of Mulmina™ mango juice was evaluated using animal models which help to simulate human allergic responses and provide insights into the potential therapeutic effects of the juice. The results from these studies indicate that Mulmina™ mango juice significantly reduces allergic symptoms, which can be attributed to its rich composition of anti-inflammatory and antioxidant phytochemicals.

CONCLUSION

This study demonstrates that Mulmina™ mango juice possesses significant anti-allergic properties, attributed to its rich content of bioactive compounds such as phenolic compounds, vitamins, amino acids, triterpenoids, and curcumin. These phytochemicals modulate immune responses, inhibit inflammatory mediator release, and enhance antioxidant defences,

effectively reducing allergic symptoms. Animal model studies further confirm its potential as a natural remedy for allergic conditions. Therefore, Mulmina™ mango juice shows promise as a beneficial dietary supplement for managing allergies. Future research should focus on clinical trials to validate these findings in human subjects.

CONFLICT OF INTEREST

The authors declare that there is no real conflict of interest for this article.

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