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Anti-allergic activity of German chamomile (*Matricaria recutita* L.) in mast cell mediated allergy model

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ABSTRACT

Ethnopharmacological relevance: Chamomile is most popular used medicinal plant and extensively consumed as a tea or tisanes. Traditionally this plant was used for treatment of many ailments such as allergy disorders and inflammatory mediated diseases.

Aim of the study: We investigated the effects of anti-allergic activity of *Matricaria recutita* L. on mast cell mediated allergic models.

Materials and methods: The protective effect of methanol extract of *Matricaria recutita* against compound 48/80 induced anaphylaxis and pruritis models for acute phase of hypersensitivity reactions were carried out. The late phase hypersensitivity reactions by compound 48/80 induced mast cell degranulation and histamine release from blood along with serum nitric oxide (NO), rat peritoneal fluid nitric oxide (NO) and bronchoalveolar fluid nitric oxide (NO) levels were measured.

Results: The methanol extract of *Matricaria recutita* L. showed inhibitory effects on anaphylaxis induced by compound 48/80 and significant dose dependent anti-pruritis property was observed by inhibiting the mast cell degranulation. Mast cell membrane stabilization activity was also observed in compound 48/80 induced mast cell activation. Dose dependent reduction in the histamine release, along with decreased release of serum, rat peritoneal and BAL fluid nitric oxide (NO) levels were observed.

Conclusion: These results suggest that the methanol extract of *Matricaria recutita* showed potent anti-allergic activity by inhibition of histamine release from mast cells.

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1. Introduction

Allergic diseases include asthma, rhinitis, atopic eczema and dermatitis syndrome. Its prevalence has been increasing world wide (Xie and He, 2005). Mast cell, which is constituent of virtually all organs and tissue are important mediators of inflammatory responses such as allergy and anaphylaxis. Anaphylaxis is mediated by histamine released in response to antigen cross-linking of IgE bound to FC ϵ RI on mast cells. Mast cell activation causes the process of degranulation that results in the release of mediators such as histamine, as well as a wide variety of other inflammatory mediators such as leukotrienes, prostaglandins, proteases and several pro-inflammatory and chemotactic cytokines (Kalesnikoff and Galli, 2008). In addition, allergic responses also trigger the influx and activation of a variety of cells including eosinophils and lymphocytes (Metcalf et al., 1997). Among the inflammatory mediators released from mast cells, histamine remains the best

characterized and most potent vasoactive mediator implicated in acute phase of hypersensitivity (Kim et al., 2005). Mast cell degranulation can also be elicited by non-immunologic stimulators such as neuropeptides, basic compounds, compliment components, and certain drugs (Oskeritizian et al., 2005). Compound 48/80 and polymers of basic amino acids are some of the most potent stimulator of mast cells and elicits the mast cell degranulation (Ennis et al., 1980). It has been suggested that a variety of anti-allergic compounds may inhibit histamine release by acting directly on the ion-gating mechanism to prevent movement of calcium from the extracellular environment into the cytosol (Foreman et al., 1977). The flowers of chamomile have been used against allergic diseases and still occupy an important place in traditional oriental medicine (Yoshinori et al., 2005).

Matricaria recutita L. (Asteraceae) also called German chamomile is one of the most widely used and well-documented medicinal plant in the world (Salamon, 1992). The main constituents of the plant include several phenolic compounds primarily the flavonoids apigenin, quercetin, patuletin, luteolin (Newall et al., 1996), it also contains terpenoids, chamazulene and sequiterpenes. Azulene compounds have been documented

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as anti-allergic (Nemecz, 1998). It is used externally for wounds, ulcers, eczema, gout, skin irritations, neuralgia, sciatica, rheumatic pain, hemorrhoids, mastitis and leg ulcers (Newall et al., 1996). Scientifically, *Matricaria recutita* was evaluated for neuroprotective (Chandrashekhar et al., 2010), anti-inflammatory, antiseptic and spasmolytic properties (Barene et al., 2003). In present study, we examined the effect of anti-allergic effect of *Matricaria recutita* on mast cell mediated allergic models.

2. Materials and methods

2.1. Chemicals and reagents

The compound 48/80, toluidine blue, and Griess reagent were obtained from the Sigma Chemical Co (St. Louis, MO, USA). The o-phthalaldehyde, disodium chromoglycate (DSCG) and RPMI-1640 medium were obtained from Hi-Media Laboratories Pvt Ltd, Mumbai, India. Refrigerated centrifuge (MPW-350R) from MPW Med. instrument, Warszawa, Poland and UV-Spectrophotometer (UV-1601) Shimadzu, Japan. All other chemicals and reagents used were of analytical grade.

2.2. Plant material

In the present study, capitulas *Matricaria recutita* L. were collected from the National Botanical Research Institute (NBRI), Lucknow, India during month of June 2010. Herbarium was prepared and the specimen was further identified and authenticated in Department of Botany, Basaveshwar Science College, Bagalkot, Karnataka and voucher specimen (B.Sc./Bot./14/2010) was deposited in the herbarium of the same college. All capitulas were dried at room temperature until they were free from moisture. Finally, the capitulas were subjected to pulverizer to get coarse powder and then passed through sieve #44 to get uniform powder. The sieved powder was stored in airtight high density polyethylene container before extraction. The powdered capitula were subjected to successive extraction with methanol (64–65.5 °C). After solvent was distilled off from the residue of the extraction and excess solvent was completely removed by using a rotatory flash evaporator to get concentrated, then completely dried by lypolization (Mini Lyotrap, LTE Scientific Ltd, Great Britain) and stored in airtight container under refrigeration. The obtained extract (70 g, percentage yield—11.67%) then used for anti-allergic activity.

2.3. Phytochemical screening

Phytochemical screening of methanol extract was carried out by employing the standard procedure and tests (Treas and Evans, 1989), to reveal the presence of chemical constituents such as terpenoids, flavonoids, tannins and coumarins.

2.4. Animals

Male Sprague–Dawley rats (200–250 g) and Balb/c mice (20–25 g) were obtained from the central animal house of H.S.K. College of Pharmacy & Research Centre, Bagalkot. The animals were housed under standard conditions (temperature 25 ± 1 °C, relative humidity 50–55%) for 12 h dark and 12 h night cycle respectively.

They were given standard laboratory feed (Pranava Agro Industries LTD, Sangli, Maharashtra) and water *ad libitum*. The study was conducted after obtaining clearance from the Institutional Animal Ethical Committee as per the CPCSEA guidelines (F. No. H.S.K. College of Pharmacy, Bagalkot/IAEC, Clear/2009-10/1-8).

2.5. Acute toxicity study and dose selection

The acute toxicity study was performed as per the method described by Litchfield and Wilkcoxon (1949), and LD50 was calculated accordingly. The methanol extract of *Matricaria recutita* in the dose range of 100, 200, 400, 800, 1600 and 3200 mg/kg was administered orally to different groups of mice ($n = 10$) of single dose. The animals were examined at every 30 min up to a period of 3 h and then, occasionally for additional period of 4 h, finally 24 h mortality was recorded. The mice were also observed for other signs of toxicity, such as excitation, tremors, twitches, motor co-ordination, righting reflex and respiratory changes. The mice were showed no mortality and safe even at dose 3200 mg/kg body weight. The anti-allergic activity was performed at three dose levels 100, 200 and 300 mg/kg of body weight (Chandrashekhar et al., 2010).

2.6. Anti-anaphylaxis activity

The mice were given an intraperitoneal injection of compound 48/80 at a dose of 8 mg/kg, a mast cell degranulation compound. The DSCG standard drug (10 mg/kg), and methanol extract of *Matricaria recutita* L. were administered at doses of 100, 200 and 300 mg/kg orally, 1 h prior to administration of compound 48/80 ($n = 10$). Mortality was monitored for 1 h after induction of anaphylactic shock (Jin Mu et al., 2001; Kim et al., 2005):

$$\text{Mortality (\%)} = \frac{\text{Number of dead mice}}{\text{Total number of experimental mice}} \times 100$$

2.7. Antipruritis activity

Compound 48/80, 3 mg/kg was administered subcutaneously into the base of neck on the back of mice to induce scratching behavior. DSCG at doses of 10 mg/kg and methanol extract of *Matricaria recutita* L. was given at doses of 100, 200 and 300 mg/kg were given orally, 1 h before compound 48/80 injection. The incidences of scratching behavior on the whole body and the site of injected area after administration of compound 48/80 were counted for 20 min (Zheng et al., 2001; Ishiguro et al., 2002):

$$\text{Scratching (\%)} = \frac{\text{Number of scratches in control group} - \text{Number of scratches in treated group}}{\text{Number of scratches in control group}} \times 100$$

2.8. Mast cell stabilizing activity

The DSCG at doses of 10 mg/kg and methanol extract of *Matricaria recutita* L. at doses of 100, 200 and 300 mg/kg were given to rats daily 5 days prior to the collection of mast cells. The animal is anesthetized by anesthetic ether and injected normal saline (10 ml) into peritoneal cavity. After gentle massage the peritoneal fluid was collected and transferred into test tube containing RPMI-1640 (pH 7.2–7.4). Mast cells are washed three times by centrifugation at low speed (400–500 rpm) discarding the supernatant and taking the pellet of mast cells into the medium. Mast cells from the control and treated group were incubated with compound 48/80 (1 µg/ml) at 37 °C for 10 min. After incubation, mast cells were stained with toluidine blue (0.1%) and percent of protection against degranulation was counted under high-power microscope (45×) (Singh et al., 1998). Percent protection against degranulations was calculated.

Table 1
Effect of *Matricaria recutita* extract on compound 48/80 induced pruritis and blood histamine release.

Treatment	Dose (mg/kg)	Scratching behavior		Blood histamine level	
		Number scratching behavior in mice	Percentage (%) inhibition of scratching	Blood histamine content ($\mu\text{g/ml}$)	Percentage (%) inhibition of histamine release
Normal saline	1 ml/kg, p.o	19.50 \pm 4.573	–	0.0303 \pm 0.0039	70.14
Control	1 ml/kg	244.3 \pm 37.45 ^a	–	0.1015 \pm 0.0147 ^a	–
Standard (DSCG)	10	151.5 \pm 05.45*	38.00	0.0546 \pm 0.0075**	44.52
MEM	100	119.3 \pm 12.72**	51.17	0.0623 \pm 0.0019*	38.59
MEM	200	55.67 \pm 09.461***	77.21	0.0690 \pm 0.0114	32.01
MEM	300	30.50 \pm 05.396***	87.52	0.0340 \pm 0.0033***	66.50

All the values are expressed as a mean \pm SEM, $n = 6$, ^a $p < 0.001$ as compared with normal group (Student's t -test). * $p < .05$, ** $p < .01$, *** $p < .001$ as comparison to control group (one way analysis of variance (ANOVA) followed by multiple comparison Tukey test). MEM, methanol extract of *Matricaria recutita* L. and DSCG, disodium chromoglycate.

2.9. Determination of blood histamine release

The DSCG at doses of 10 mg/kg and methanol extract of *Matricaria recutita* L. at doses of 100, 200 and 300 mg/kg were given to rats daily 5 days prior to collection of blood. The rats were anesthetized by anesthetic ether and then blood was collected by cardiac puncture and these blood sample were incubated with compound 48/80 (1 $\mu\text{g/ml}$) and residual histamine in cells was released by disrupting the cells with perchloric acid and centrifugation at $400 \times g$ for 5 min at 4 °C. The histamine content was determined by o-phthalaldehyde spectrofluorimetric method (Shore et al., 1959).

2.10. Measurement of serum nitric oxide level

The standard drug (DSCG) at dose of 10 mg/kg and methanol extract of *Matricaria recutita* at doses of 100, 200 and 300 mg/kg were given to rats daily 5 days prior to collection of blood. The rats were anaesthetized by anesthetic ether and then blood was collected from retro-orbital, centrifuged at 500 rpm for 5 min then equal volume of serum, Griess reagent (pH 2) was added and incubated for 15 min at 37 °C. The normal group sample was incubated with normal saline, control and extract treated groups were incubated with compound 48/80 (1 $\mu\text{g/ml}$) and after completion of incubation period, the absorbance was measured at 546 nm (Mc Cauley et al., 2005; Ganapaty et al., 2010).

2.11. Measurement of rat peritoneal fluid nitric oxide

The peritoneal fluid was collected same as stated above (Section 2.6) in mast cell stabilizing activity. The equal volume of peritoneal fluid, Griess reagent (pH 2) and 40 μl of glycine buffer was added and incubated for 15 min at 37 °C, then the incubated sample was centrifuged and the supernatant was used for measurement of absorbance. The normal group sample was incubated with normal saline, control and extract treated groups were incubated with compound 48/80 (1 $\mu\text{g/ml}$) at 37 °C for 15 min and the absorbance was measured at 546 nm (Mc Cauley et al., 2005).

2.12. Bronchoalveolar (BAL) fluid nitric oxide level

The BAL fluid was collected and centrifuged, the control and treated groups were incubated with compound 48/80, acidic Griess reagent (pH 2) and 40 μl of glycine buffer was added for 15 min at 37 °C and the absorbance was measured at 546 nm.

2.13. Statistical analysis

All the data presented as mean \pm SEM. The significance of difference in means between control and treated animals for different parameters was determined by using one-way analysis of variance

(ANOVA) followed by multiple comparison Tukey test. The $p < 0.05$ is considered as significant.

3. Result

3.1. Effect of methanol extract of *Matricaria recutita* L. on anaphylaxis activity

There was potential protection from mortality induced by compound 48/80 at dose of 10 mg/kg of DSCG, exhibited 70% protection and treated groups at doses 100, 200 and 300 mg/kg showed 50, 50 and 60% of protection from mortality respectively (results are not shown in table).

3.2. Effect of *Matricaria recutita* L. extract on compound 48/80 induced pruritis

Percentage of scratching behavior was significantly reduced in mice treated with DSCG ($p < 0.05$) and methanol extract of *Matricaria recutita* ($p < 0.01$ to $p < 0.001$) as compared to control group. Standard group showed 38% of protection, treated groups 100, 200 and 300 mg/kg showed 51.17, 77.21 and 87.52% of protection from scratching incidences respectively. The results are summarized in Table 1.

3.3. Effect of methanol extract of *Matricaria recutita* L. on mast cell degranulation

There was significant ($p < 0.001$) protection from mast cell degranulation induced by compound 48/80. Standard (DSCG) group showed 67.75% of protection and treated groups at doses 100, 200 and 300 mg/kg showed 51.92, 65.42 and 73.33% of protection from mast cell degranulation respectively. The results are summarized in Fig. 1.

3.4. Effect of *Matricaria recutita* L. extract on compound 48/80 induced on blood histamine release

The control group animals showed significant ($p < 0.001$) elevated histamine release in blood as compared to normal group. In contrast, the treatment with methanol extract of *Matricaria recutita* L. were showed significantly ($p < 0.05$ to $p < 0.001$) reduced histamine content in the blood as compared to the control group. The results are summarized in Table 1.

3.5. Effect of *Matricaria recutita* L. extract on compound 48/80 induced serum, peritoneal fluid and BAL fluid nitric oxide levels

The control group animal showed significant ($p < 0.001$) elevated nitric oxide release from serum, peritoneal and BAL fluid as compared to normal group. In contrast, the DSCG and treatment with methanol extract of *Matricaria recutita* L. were showed significantly

Table 2Effect of *Matricaria recutita* L. extract on compound 48/80 induced release serum, BAL and rat peritoneal fluid nitric oxide.

Treatment	Dose (mg/kg)	Serum nitric oxide	BAL nitric oxide	RPF nitric oxide
Normal saline	1 ml/kg; p.o	3.150 ± 0.1607	2.750 ± 0.6903	1.183 ± 0.1641
Control	1 ml/kg	8.333 ± 1.0464 ^a	17.92 ± 3.459 ^a	3.733 ± 0.3127 ^a
Standard (DSCG)	10	2.800 ± 0.1324 ^{***}	5.200 ± 0.321 ^{***}	1.321 ± 0.1424 ^{***}
MEM	100	6.483 ± 1.1652	13.78 ± 1.077	2.033 ± 0.2011 ^{***}
MEM	200	4.500 ± 0.5550 [*]	8.400 ± 1.111 ^{**}	1.433 ± 0.2011 ^{***}
MEM	300	3.200 ± 0.3464 ^{***}	3.600 ± 0.831 ^{***}	1.450 ± 0.2814 ^{***}

All the values are expressed as a mean ± SEM, n = 6, ^ap < 0.001 as compared with normal group (Student's *t*-test). *p < .05, **p < .01, ***p < .001 as comparison to control group (one way analysis of variance (ANOVA) followed by multiple comparison Tukey test). MEM, methanol extract of *Matricaria recutita* L. and DSCG, disodium chromoglycate.

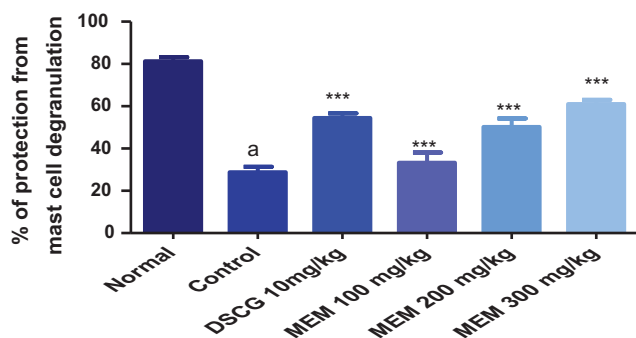


Fig. 1. Effect of *Matricaria recutita* extract on compound 48/80 induced mast cell degranulation in rats. All the values are expressed as a mean ± SEM, n = 6, ^ap < 0.001 as compared with normal group and *p < .05, **p < .01, ***p < .001 as comparison to control group. MEM, methanol extract of *Matricaria recutita* L. and DSCG, disodium chromoglycate.

reduced levels of serum ($p < 0.05$ to $p < 0.001$), peritoneal ($p < 0.01$ to $p < 0.001$) and BAL fluid nitric oxide ($p < 0.001$) as compared to the control group. The results are summarized in Table 2.

4. Discussion

Chamomile is one of the most commonly consumed single ingredient herbal tea. This herbal preparation is used in traditional cultures, the therapeutic uses and purported health benefits of chamomile are based largely on folklore rather than on scientific evidences. The present scientific study substantiated that *Matricaria recutita* L. has significant anti-allergic properties. *Matricaria recutita* L. inhibited compound 48/80 induced systemic allergic reaction. In short period of treatment (5 days) we have observed a significant protection from mast cell degranulation and also significant decrease in the release of allergic mediators like blood histamine, serum, rat peritoneal and BAL fluid nitric oxide levels.

Mast cells play a key role in the immediate type of allergic reactions through the release of numerous mediators and cytokines. Mast cell degranulation also can be elicited by the synthetic compound 48/80, and it has been used as a direct and convenient reagent to study the mechanism of anaphylaxis (Ennis et al., 1980). Numerous reports established that stimulation with compound 48/80 initiates the activation of signal transduction pathway, which leads to histamine release. The compound 48/80-induced anaphylactic shock is due to the release of vasoactive substances such as histamine from mast cells and basophiles (Amir and English, 1991). NF- κ B transcription factor is reported to be crucial to the initiation and maintenance of inflammatory reactions by the modulating the several pro-inflammatory mediators, including TNF- α , and IL-6. The above nuclear factor activation and overexpression are response to the release of inflammatory mediator histamine by degranulation. The methanol extract of chamomile showed

significant dose dependent protection (100–300 mg/kg) against compound 48/80 induced anaphylaxis.

Antipruritis activity was evaluated by observing incidence of scratching behavior by subcutaneous administration of compound 48/80. Compound 48/80 administered control group showed significant increase in number of scratching and thought to be associated with release of histamine from mast cell degranulation. In contrast, administration of *Matricaria recutita* L. showed dose dependently significant inhibition of scratching.

Previous studies indicated that compound 48/80 and other polybasic compounds directly activate G-proteins. Compound 48/80 increases the permeability of the lipid bilayer membrane by causing the perturbation in the membrane. The intracellular calcium pathways are crucial to the degranulation of mast cells. Agents that stimulate an intracellular calcium level have been shown to induce mast cell degranulation (Tasaka et al., 1986). Calcium movements in mast cells represent a major target for effective anti-allergic drugs, as this is an essential event linking stimulation to secretion. The extract of *Matricaria recutita* L. showed that attenuation of compound 48/80 induced intracellular calcium in mast cells was strongly speculated that decreased intracellular calcium involved in the inhibitory effect of histamine release and might have membrane stabilizing activity through inhibition of G-protein activation (Shina et al., 2005). Phytochemical screening of *Matricaria recutita* showed the presence of flavonoids, glycosides, tannins, terpenoids and coumarins. Tannins are reported to possess mast cell stabilizing, anti-allergic and anti-histaminic activities (Gupta et al., 1968). Several flavonoids have been shown to bronchodilator activity and smooth muscle relaxant (Hazekamp et al., 2001). The flavonoids including apigenin and luteolin were main constituents of *Matricaria recutita* known to inhibit basophil histamine release and neutrophil betagluuronidase release, and there by act as *in vitro* antiallergic activity (Pathak et al., 1991). These flavonoids also inhibited the histamine release induced by 48/80 (Bellanti, 1971).

Mast cells are important in the numerous physiological processes of homeostasis and disease. Nitric oxide (NO) is a diatomic radical produced by nitric oxide synthase (NOS), and has cytotoxic properties. NO can influence many mast cell functions including adhesion, degranulation, early mediator release and leukotriene production (Mc Cauley et al., 2005). During immune and inflammatory allergy conditions, NO is generated at relatively high and sustained levels by the inducible form of NOS-2 (Coleman, 2002). Nitric oxide might act as a source of free radicals, leading to damage of tissue and infiltration of lymphocytes and inflammatory reactions. Methanol extract of *Matricaria recutita* L. showed significant ($p < 0.05$ to $p < 0.001$) inhibition of nitric oxide levels in serum, rat peritoneal and BAL fluids.

Hence, antiallergic activity of chamomile may be due to presence of tannins and flavonoids. These results completely justify the folkloric use of *Matricaria recutita* to treat allergic diseases. In conclusion, methanol extract of *Matricaria recutita* has antiallergic activity and potential to stabilize mast cells. In

addition, further studies are required to establish its mechanism of action.

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