

Diuretic efficacy of *Matricaria chamomilla* in normotensive and salt-induced hypertensive rats

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Abstract

Background and objectives: Traditionally Chamomile (*Matricaria chamomilla* L.) has various medicinal uses. It has soothing, calming, sedative, and anti-inflammatory effects. The present study was designed to evaluate the effectiveness of decoction of Chamomile on urine flow rate, urinary and serum electrolyte concentration, urinary sodium and potassium excretion rates, urine and serum creatinine concentration, glomerular filtration rate, and the percentage of reabsorbed of filtered sodium, in normal and salt loaded hypertensive rats.

Methods: The study was carried out on 30 rats, which were divided into two groups. The first group involved twelve normotensive rats and were subdivided into two subgroups each of 6 rats. The first subgroup served as a control group. The second subgroup received decoction Chamomile orally for 3 weeks. The second group included 18 induced hypertensive rats and were divided into 3 subgroups each of 6 rats. The first subgroup served as a positive control. The second and third subgroups received decoction of Chamomile and of Chlorthalidone respectively.

Results: Chamomile decoction produced a significant increase in urine flow, Sodium excretion rate, Glomerular filtration rate and urinary creatinine level without significant effects on blood pressure, heart rate, and serum creatinine and blood urea in normal rats. Unlike Cholothalodone Chamomile decoction did not induce diuresis and has no significant effects on blood pressure in normal and hypertensive rate. However, the same dose of chamomile significantly increased serum potassium level in both normal and hypertensive rats.

Conclusion: Chamomile has mild diuretic activity in normal rats and its effects resemble that of potassium sparing diuretics.

Key: *Matricaria chamomilla*, Cholothalodone, Diuretic, Hypertensive rats

Introduction:

Diuretics have been used effectively to treat millions of hypertensive patients. They reduce both systolic and diastolic blood pressures in the most of hypertensive patients, They are administered alone or in combination with other antihypertensive agents form the basis of therapy for the majority of hypertensive patients ¹. Because of their efficacy, low cost, and low side effects profile, diuretics are first choice to be prescribed for patients with hypertension, as well as their synergistic effect when combined with other antihypertensive agents; and their usefulness in patients with heart failure ².

Traditionally, in most countries all over the world many plants have been used for their diuretic effect, for example the ripe fruits of *Carum carvi* and the leaves of *Tanacetum vulgare* are two widely available plant materials, that are used as diuretics in the Moroccan traditional medicine ³. *Urticaria dioica*, is another example, which is used by Kurdistan folks ⁴.

Many other herbal plants exerting diuretic property, were traditionally used, e.g. *Mangifera indica*, *Mimosa pudica*, *Lipidium sativum*, and *Achyranthes aspera* ⁵. *Doradilla* that has a long history in the Mexican traditional system of medicine for gall and renal stones, through its diuretic action ⁶.

Chamomile or *Matricaria chamomilla* L. (*M. chamomilla*) is usually referred to as the "star among medicinal species" a well-known medicinal plant species from the Asteraceae family. It has multitherapeutic, cosmetic, and nutritional values have been established through years of traditional and scientific uses and researches, it is one of the highly favored and much used medicinal plant in folk and traditional medicine ⁷.

Matricaria Chamomilla has a wide range of therapeutic actions; soothing, calming, sedative, relaxation, anti-inflammation, treating indigestion, hay fever, asthma, morning sickness, eczema, and sore nipples ⁸. About 120 chemical constituents have been identified in chamomiles as secondary metabolites, including 28 treptinoids, 36 flavonoids, and 52 additional compounds with pharmacological activity ⁹.

Because little information is available about the activity of *M. chamomilla* to produce diuresis, therefore this study is undertaken to evaluate the activity of *M. chamomilla* decoction as a diuretic agent in normotensive and hypertensive animal model.

Materials and Methods

Preparation of *M. chamomilla* decoction.

Dry *M. chamomilla* flowers were weighed and crushed to powder with a marble pestle and mortar, then 15% w/v (150 g was added in 1000 ml of distilled water) heated in a steel kettle and allowed to boil for 15 minutes. The flask was then placed on a shaker for four hours, at room temperature. After shaking, the suspension was filtered through a series of filter papers to avoid the bacterial contamination and stored at 4°C until use¹⁰. After that, it's filled with distilled water up to 1000 ml for making up the desired volume for dosage calculation, each rat was give 3 ml of the decoction (1.3g/kg/day) by oral gavages every morning during the 21 days of the study.

Experimental Design.

Diuretic activity of prepared *M. chamomilla* decoction was studied on 30 adult male Wistar rats, weighing 300–350 gram which were divided into two groups. The first group involved twelve normotensive rats, six rats sacrificed as a negative control and the other six rats received 3ml 15% decoction of *M. chamomilla* every day during the 21 days of study period. The second group involved 18 hypertensive rats. Hypertension was induced by sodium load diet and water¹¹. The hypertensive rats were subdivided into three subgroups, each of six rats. The first subgroup served as a positive control. The second and third subgroups received 3 ml of 15% decoction *Matricaria Chamomilla* by oral gavages, and 1 ml (5mg/kg) chlorthalidone respectively. All the rats were exposed to the same environment.

Group I: Normal rats served as negative control.

Group II: Normal rats treated with decoction *M. chamomilla* (1.3 g/kg/day).

Group III: Hypertensive rats served as positive control.

Group IV: Hypertensive rats given 15% decoction *M. chamomilla* (1.3 g/kg/day).

Group VI: Hypertensive rats given chlorthalidone (5 mg/Kg).

Sample collections.

Urine samples.

Urine was collected 24 hour based, and measured after dosing by putting the rats in the metabolic cages. Then urine volume of each rat was measured, and put in a urine container and the samples were taken to the laboratory for creatinine and electrolytes in urine (sodium and potassium) analysis.

Blood samples.

At the end of drug and herbal treatment, all the rats were fasted overnight allowed free access to water. At the morning of the next day, the rats were anesthetized by a combination of ketamine in a dose of 75mg/kg with xylazine in a dose of 10 mg/kg intraperitoneally (IP) (Gallaly, 2012), then

blood samples were taken from their hearts by direct cardiac puncture by the needle of a plastic syringe.

Statistical Analysis

The results of serum and urine electrolytes concentrations, serum and urine creatinine concentration, serum urea concentration, urine flow, sodium excretion rate, potassium excretion rate, glomerular filtration rate, percentage of sodium reabsorbed of filtered load, blood pressure and heart rate of the rats were analyzed statistically using SPSS software program package 21 and are expressed as mean \pm standard errors of means ($M \pm SEM$). Data analysis was made using one-way analysis of variables (ANOVA). Comparison was made between groups using Duncan test and unpaired student t-test. A p value of ≤ 0.05 was considered statistically significant.

Results

Effects of *M. chamomilla* decoction (15%) on blood pressure and heart rate in normal rats.

The blood pressure of normal rats treated with *M. chamomilla* was non-significantly higher than the normal control rats (Table 1).

Table 1 Effects of *M. chamomilla* decoction (15%) on blood pressure and heart rate in normal rats.

Parameters	Normal Rats (n=6)	Normal Rats /MC (n=6)	P value
Blood Pressure (mmHg)	106 \pm 4	110 \pm 4	0.347
Heart Rate (Beats/minute)	333 \pm 41	359 \pm 10	0.537

*MC: *Matricaria chamomilla*.

Effects of *M. chamomilla* decoction (15%) on urine flow, sodium excretion rate, potassium excretion rate, GFR and % Na⁺ reabsorption of filtered load in normal rats.

The urine flow of the normal rats treated with 15% decoction of *M. chamomilla* was significantly higher than the normal rats that did not receive the plant decoction, (Table 2). Sodium excretion rate, was significantly increased in normal rats received *M. chamomilla* decoction. There was a slight and non-significant elevation in Potassium excretion rate of normal rats received *M. chamomilla* decoction, (Table 2). Glomerular filtration rate was significantly increased in *M. chamomilla* treated rats by four folds in comparison to non-treated normal rats. The percentage of sodium ion reabsorption was not significantly increased in the normal rats following daily administration *M. chamomilla* decoction, (Table 2).

Table 2. Effects of *M. chamomilla* decoction (15%) on urine flow, sodium excretion rate, potassium excretion rate, GFR and % Na⁺ reabsorption of filtered load in normal rats.

Parameters	Normal Rats (n=6)	Normal Rats /MC (n=6)	P value
Urine flow (ml/min/kg)	0.0144 ±0.0015	0.0348 ±0.0037	0.001
Na ⁺ excretion rate (μEq/min/kg)	2.98 ±0.54	11.5 ±1.43	0.001
K ⁺ excretion rate (μEq/min/kg)	0.7 ±0.21	1.11 ±0.12	0.057
GFR (ml/min/kg)	0.20 ±0.04	2.76 ±0.44	0.04
%Na ⁺ Reabsorption of filtered load	88.5 ±2.15	96.7 ±0.5	0.087

* MC: *Matricaria chamomilla*, GFR: Glomerular filtration rate.

Effects of *M. chamomilla* decoction (15%) on urinary sodium, potassium and creatinine concentration in normal rats.

Urinary Na⁺ concentration of rats treated with *M. chamomilla* decoction was increased significantly in comparison to normal rats who did not receive, while urinary K⁺ concentration was slightly and non-significantly decreased (Table 3). Urinary creatinine concentration was significantly increased in *M. chamomilla* treated rats compared to the non-treated rats (Table 3).

Table 3. Effects of *M. chamomilla* decoction (15%) on urinary electrolytes and creatinine concentrations in normal rats.

Parameters	Normal Rats (n=6)	Normal Rats/MC (n=6)	P value
Urinary Na ⁺ (mEq/L)	200.16 ±17.93	327.16 ±16.81	0.008
Urinary K ⁺ (mEq/L)	46.36 ±12.5	32.16 ±0.6	0.299
Urinary Cr. (mg/dl)	8.27 ±1.06	44.16 ±2.3	0.000

*MC: *Matricaria chamomilla*.

Effects of *M. chamomilla* decoction (15%) on serum electrolytes and serum urea and creatinine concentration in normal rats.

Serum sodium (Na⁺) concentration of normal rats treated with *M. chamomilla* was slightly and non-significantly decreased, whereas serum potassium (K⁺) level was significantly increased, (Table 4). Daily administration of *M. Chamomilla* had no significant effect on serum creatinine (S. Cr.) and serum urea concentrations in normal rats (Table 4).

Table 4. Effects of *M. chamomilla* decoction (15%) on serum electrolytes and serum urea and creatinine concentration in normal rats.

Parameters	Normal rats (n=6)	Normal rats/ MC (n=6)	P value
S. Na ⁺ (mEq/L)	142.3 ±0.84	138.5 ±2.04	0.279
S. K ⁺ (mEq/L)	4.28 ±0.09	6.4 ±0.397	0.022
S. Cr. (mg/dl)	0.6 ±0.44	0.58 ±0.65	0.28
S. Urea (mg/dl)	43.5 ±3.33	20.3 ±2.29	0.423

* MC: *Matricaria chamomilla*.

Effects of *M. chamomilla* decoction (15%) and CLTD (5 mg/kg) on blood pressure and heart rate in hypertensive rats.

Matricaria Chamomilla decoction did not reduce blood pressure of hypertensive rats, but it significantly reduced the heart rate. Whereas chlorthalidone could significantly decrease both blood pressure and heart rate of hypertensive rats (Table 5).

Table 5. Effects of *M. chamomilla* decoction (15%) and CLTD (5mg/kg) on blood pressure and heart rate in hypertensive rats.

Parameters	Hypertensive Rats (n=6)	Hypertensive/MC (n=6)	Hypertensive/CLTD (n=6)
Blood Pressure (mm.Hg)	121 ±1.86 a	123±3.79 a	107± 1.83 b
Heart Rate (bpm)	407 ±11.66 a	355 ±10.87 b	337 ±11.54 b

MC: *Matricaria Chamomilla*. CLTD: Chlorthalidone.

Effects of *M. chamomilla* decoction (15% W/V) and CLTD (5 mg/kg) on urine flow, sodium excretion rate, potassium excretion rate, GFR and % Na⁺ reabsorption of filtered load in hypertensive rats.

Urine flow of hypertensive rats receiving 15% decoction of *M. chamomilla* was slightly and non-significantly increased. Whereas in hypertensive rats that received chlorthalidone, urine flow was significantly increased (Table 6.).

Urinary sodium and potassium excretion rates of the hypertensive rats receiving *M. chamomilla* decoction was non-significantly changed, while CLTD significantly increased both urinary sodium and potassium excretion rates in hypertensive rats. (Table 6). Glomerular filtration rate in hypertensive rats receiving *M. chamomilla* or chlorthalidone was non-significantly changed, as shown in Table (3.6). Furthermore, both *M. chamomilla* and chlorthalidone had no detectable effects on % Na⁺ reabsorption of filtered load in the hypertensive rats Table (6).

Table 6. Effects of *M. chamomilla* decoction (15%) and CLTD (5 mg/kg) on urine flow, sodium excretion rate, potassium excretion rate, GFR and % Na⁺ reabsorption of filtered load in hypertensive rats.

Parameters	Hypertensive rats (n=6)	Hypertensive/ MC (n=6)	Hypertensive/ CLTD (n=6)
Urine flow (ml/min/kg)	0.0283± 0.0044 a	0.0316± 0.0043 a	0.055 ± 0.0073 b
Na ⁺ excretion rate (µEq/min/kg)	9.2±1.69 a	9.26 ±1.42 a	16.5 ±2.15 b
K ⁺ excretion rate (µEq/min/kg)	0.74 ±0.14 a	0.958± 0.13 a	1.66±0.18 b
GFR (ml/min/kg)	0.99 ±0.18 a	2.24 ±0.5 a	2.2 ±0.7 a
% Na ⁺ reabsorption of filtered load	93.56 ±0.59 a	95.59±1.37 a	91.96 ± 1.6 a

MC: *Matricaria chamomilla*. CLTD: Chlorthalidone, GFR: glomerular filtration rate.

Effects of *M. chamomilla* decoction (15%) and CLTD (5mg/kg) on urinary sodium, potassium and creatinine concentration in hypertensive rats.

Urinary Na⁺ concentration of hypertensive rats treated with *M. chamomilla* or chlorthalidone were non-significantly changed. Table (7). Whereas, urinary K⁺ concentrations of the hypertensive rats received chamomile or chlorthalidone were slightly and significantly increased Table. (7).

Urinary creatinin concentration in hypertensive rats that received *M. chamomilla* decoction or chlorthalidone were significantly higher than that of non-treated group. Table (7).

Table 7. The effects of *M. chamomilla* decoction (15%) and CLTD (5 mg/kg) on urinary electrolytes and creatinin concentration in hypertensive rats.

Parameters	Hypertensive Rats (n=6)	Hypertensive/MC (n=6)	Hypertensive/CLTD (n=6)
Urinary Na ⁺ (mEq/L)	319.83±14 a	290 ±9.29 a	300 ±5.73 a
Urinary K ⁺ (mEq/L)	26 ±1.8 a	30.3 ±0.88 b	30.6 ±1.02 b
Urinary Cr. (mg/dl)	22 ±1.77 a	60 ±9.7 b	39 ±10.27 ab

Effects of *M. chamomilla* decoction (15%) and CLTD (5 mg/kg) on serum electrolytes and serum urea and creatinine concentration in hypertensive rats.

Serum Na⁺ concentrations of hypertensive rats treated with *M. chamomilla* and chlorthalidone were significantly lower than non-treated hypertensive rats. Table (8).

Serum K⁺ concentration of the hypertensive rats received *M. chamomilla* was significantly increased, but in chlorthalidone treated rats, serum potassium concentration non significantly has been changed (Table 8).

Serum Creatinine concentration in hypertensive rats that received *M. chamomilla* decoction was non-significantly higher than the non-treated group. While in hypertensive rats receiving chlorthalidone, serum creatinine was significantly higher than the non-treated group (Table 8).

Serum urea concentration in hypertensive rats treated with *M. chamomilla* was non- significantly increased, whereas in chlorthalidone treated group the serum urea concentration was increased significantly (Table 8).

Table 8. Effects of *M. chamomilla* decoction (15%) and CLTD (5mg/kg) on serum electrolytes and serum urea and creatinine concentration in hypertensive rats.

Parameters	Hypertensive Rats (n=6)	Hypertensive/MC (n=6)	Hypertensive/CLTD (n=6)
S. Na ⁺ (mEq/L)	146.5 ±0.88 a	135 ±2.65 b	135.8± 0.54 b
S. K ⁺ (mEq/L)	3.85 ±0.07 a	5.38 ±0.43 b	3.98 ± 0.08 a
S. Cr. (mg/dl)	0.63±0.016 a	0.96±0.2 ab	1.11± 0.17 b
S. Urea (mg/dl)	20 ±0.83 a	35± 6.8 a	40.83 ±6 b

*MC: *Matricaria chamomilla*. CLTD: Chlorthalidone.

Figure 3.12 Effect of *M. chamomilla* decoction (15%) and CLTD (5mg/kg) on serum sodium concentration in hypertensive rats.

Discussion.

In this experimental animal model, normal and hypertensive rats were used in order to investigate the effects of *M. chamomilla* and CTLD on the measured parameters for instance total urine volume, urine and serum electrolytes concentration, and urinary potassium and sodium excretion rate.

In this study urine flow of normal rats significantly increased after receiving 15% *M. chamomilla*. This increase in urine flow by this plant decoction could be linked to a number of possible mechanisms, it might be because of inhibition of sodium reabsorption, hence urinary sodium concentration and urinary excretion rate of sodium is increased significantly, however it is not related to the inhibition of antidiuretic hormone¹², as urine Na⁺ concentration and excretion rate were increased significantly. Therefore, it can be suggested that the diuretic effect of *M. chamomilla* is saluretic type, which indicates that the plant decoction has inhibited sodium reabsorption from the renal tubules

In this study, glomerular filtration rate of normal rats receiving *M. chamomilla* was significantly increased. This effect could be related to blocking of adenosine (A1) receptor, like theophylline, therefore it increases urine output through increasing GFR and blocking NaCl reabsorption in the proximal tubule and collecting duct^{13 14}.

Moreover, this rise in GFR induced by *M. chamomilla* decoction could be related to active substances which may dilate afferent renal arterioles as do many calcium channel antagonists for example nifedipine, nicardipine, and verapamil¹⁵, or constricting renal efferent arterioles, In the

efferent arteriole, Ang II appears to stimulate Ca^{2+} entry via store-operated Ca^{2+} influx (Loutzenhiser and Loutzenhiser, 2000), resulting in an increase in GFR (Hall, 2011).

In the present study, *M. chamomilla* decoction (15%) non significantly increased the percentage of sodium reabsorption of filtered load of normal rats, because of increased sodium filtration as a result of increased GFR.

Serum sodium concentration was not significantly changed as plasma concentration of Na^+ should remain constant due to effect of various hormones and enzymes, and because of osmotic properties of plasma, as plasma osmolality is determined by plasma sodium ¹⁶.

In normal rats that administered *M. chamomilla* decoction urinary excretion rate of potassium was non-significantly increased, due to the rise in urine flow, but their urinary potassium concentration was non-significantly decreased. This indicates that *M. chamomilla* constituents increase sodium excretion more than potassium. On the other hand, *M. chamomilla* decoction significantly increased serum potassium concentration of normal rats, that it could cause hyperkalemia.

This diuretic activity of *M. chamomilla* is not attributed to blocking of aldosterone secretion because this plant and unlike spironolactone ¹⁷, its diuretic activity was appeared after two hours. While the aldosterone antagonist's diuretic effect usually appears after longer time, because they compete aldosterone for mineralocorticoid receptor, which is an intracellular receptor of the nuclear receptor family located in the kidneys, it modulates DNA transcription, causing synthesis of protein mediators as the mechanism of gene transcription, thereby inhibiting distal Na^+ retention and K^+ secretion ¹⁸.

This increase in serum potassium indicates that the diuretic effect of *M. chamomilla* does not resemble the action of the loop diuretic, such as furosemide, which acts in the thick ascending limb of loop of Henle where it acts by inhibiting the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transport carrier in the luminal membrane, in which it increases the urine output followed by increased urinary excretion of electrolytes, mainly Na^+ , K^+ , and Cl^- (HL *et al.*, 2015). Therefore, it can be suggested that the diuretic activity of extract could be resemble the directly acting potassium-sparing diuretics such as amiloride and triamterene (Tamargo *et al.*, 2014), as they act on the late distal tubules and collecting ducts, inhibiting Na^+ reabsorption by blocking luminal sodium channels and decreasing K^+ excretion ¹⁹. This could be related to high flavonoids content, that's similar to potassium sparing diuretics ²⁰.

In the current study, blood urea and serum creatinine of normal rats administered chamomile decoction were non-significantly decreased. Whereas urine creatinine concentration was significantly increased. These indicate that *M. chamomilla* extract is safe in renal diseases and has beneficial effects on kidney function (Schneider *et al.*, 2016).

Studies that have done in last decades on plants to investigate their diuretic activity have demonstrated that diuretic effect of the plants could be attributed to several compounds such as

flavonoids, saponins or organic acids, ²¹. There is a relationship between the presence of these polar secondary metabolites and their diuretic activity, which can produce diuresis they could have contact with renal tissues ²².

There are several mechanisms that contribute to the hypertensive effect of dietary salt, including water and salt retention, vascular abnormalities, and/or neurogenically mediated increases in peripheral resistance ²³. There are sequential steps by which salt intake influences arterial blood pressure. They include an effect on plasma sodium concentration and extracellular fluid volume (ECF). The greater rise in plasma sodium of sodium loaded rats, is due to a defect in the kidney's ability to excrete salt and to regulate extracellular fluid volume ²⁴.

In the current study, urine flow of hypertensive rats receiving 15% *M. chamomilla* decoction was non-significantly increased. Which indicates that chamomile may have mild diuretic activity? In hypertensive rats that received chlorthalidone, urine flow was significantly increased as a result of increased water and sodium excretion rate, because it is a benzothiazide, which is a diuretic that exerts its action by blocking the Na⁺ –Cl⁻ cotransporter in the luminal membrane of the distal convoluted tubule leading to a modest natriuresis and diuresis respectively²⁵. However, urinary sodium concentration of hypertensive rats received *M. chamomilla* or chlorthalidone was non-significantly decreased.

In this study, GFR of hypertensive rats that received *M. chamomilla* decoction or CLTD, was non-significantly increased. Neither chamomile nor chlorthalidone had detectable effect on the percentage of reabsorbed sodium of filtered load.

In this study hypertensive rats received CLTD or *M. chamomilla* decoction significantly decreased serum sodium concentration. Because hyponatremia is seen within the first weeks of the start of chlorthalidone treatment (Liamis *et al.*, 2016), this effect is related to inhibition of sodium reabsorption in the renal tubules.

In addition to hyponatremia, hypokalemia was seen in CLTD treated hypertensive rats, and this thiazide-induced hypokalemia is related to the delivery of large amount of Na⁺ in the late distal tubule and collecting duct and this promotes a transcellular exchange (transcellular shift) between K⁺ and Na⁺ as chlorothiazides inhibit sodium reabsorption only in distal tubules²⁶.

In the current study, urinary creatinine concentration of hypertensive rats received *M. chamomilla* decoction was significantly increased. However, their serum creatinine and serum urea have not been changed significantly. This indicates that *M. chamomilla* is safe during renal disorders ²⁷. Serum creatinine and blood urea of hypertensive rats treated with chlorthalidone were slightly significantly increased but it was within normal range.

In this study unlike chlorthalidone, administration of *M. chamomilla* had no significant effect on blood pressure of neither normal nor hypertensive rats. As it possesses a mild diuretic activity, and could not counteract the hypertensive effects of sodium load. However, it significantly decreased HR of hypertensive rats. This decrease in heart rate has no effects on blood pressure, as heart rate and unlike to an increase in cardiac contractility, it has minimum effects on maintaining blood pressure¹³. This negative chronotropic effect of chamomile could be attributed to the direct effect of some its active constituents on SA node, like ivabradine which has been shown to have similar effects on HR in other species including rabbits, rats, dogs, and human

Conclusion: Chamomile has mild diuretic activity in normal rats and its effects resemble that of potassium sparing diuretics.

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