EFFECT OF CHAETHOMELLIC ACID ON RENAL FUNCTION IN A RAT MODEL OF CHRONIC RENAL FAILURE

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INTRODUCTION

Chaethomellic acid (AC) is a highly specific inhibitor of ras farnesyl-protein transferase. The aim of this study has been to evaluate the effect of chronic treatment with chaethomellic acid (CA) on the renal function of rats with renal failure induced by renal mass reduction.

MATERIALS AND METHODS

Animal care and treatment were conducted in conformity with institutional guidelines that are in compliance with international laws and politics. Male Wistar rats were subjected to 5/6 nephrectomy (RMR) or sham-operated (SO). One week after surgery, rats have been randomized and placed in four experimental groups: RMR: RMR rats without treatment (n=13); RMR+AC: RMR rats treated with AC (n=13); SO: SO rats without treatment (n=13); SO+AC: SO rats treated with AC (n=13). AC was intraperitoneally administered in a dose of 0.23 µg/Kg three times a week for six months. Creatinine, blood urea nitrogen (BUN), electrolytes and protein were measured in serum and/or urine by routine laboratory techniques. The differences between groups were evaluated by one-way analysis of variance (ANOVA) followed by Bonferroni *post hoc* tests. All data are presented as the mean ± SD and were considered significant at $p<0.05$.

RESULTS

Renal function parameters are shown in table 1. BUN (figure 1), creatinine (figure 2) and urinary protein excretion (figure 3) were significantly lower and creatinine clearance (figure 4) was significantly higher in the SO and SO+AC groups when compared with the RMR and RMR+AC groups. There were no significantly differences in creatinine, urinary protein excretion and creatinine clearance between the RMR and RMR+AC groups. However, the RMR+AC group showed significantly lower BUN and lower creatinine and urinary protein excretion, and higher creatinine clearance than the RMR group.

Table 1: Effect of chaethomellic acid on renal function parameters after renal mass reduction.

Parameters	SO (n = 13)	SO+AC (n = 13)	RMR (n = 12)	RMR+AC (n = 8)	ANOVA	POST HOC (1)
Urinary Flow (µl/min.)	Md = 0,010 M = 0,011 SD = 0,002	Md = 0,009 M = 0,009 SD = 0,003	Md = 0,027 M = 0,029 SD = 0,008	Md = 0,023 M = 0,025 SD = 0,009	F(3,42) = 34,729 p < .001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC**
Sodium (mmol/l)	Md = 144,600 M = 145,170 SD = 1,831	Md = 143,960 M = 142,299 SD = 6,784	Md = 145,735 M = 146,957 SD = 4,218	Md = 147,245 M = 146,388 SD = 3,569	F(3,42) = 2,497 p = .073	
Potassium (mmol/l)	Md = 4,810 M = 4,808 SD = 0,355	Md = 4,710 M = 4,511 SD = 0,662	Md = 5,230 M = 5,275 SD = 0,472	Md = 4,820 M = 4,849 SD = 0,408	F(3,42) = 4,964 p = .005	SO+AC vs. RMR**
Chloride (mmol/l)	Md = 101,190 M = 102,522 SD = 4,268	Md = 101,340 M = 99,715 SD = 7,811	Md = 104,535 M = 105,264 SD = 5,276	Md = 108,670 M = 107,284 SD = 6,241	F(3,42) = 3,186 p = .033	SO+AC vs. RMR+AC*
Calcium (mg/dl)	Md = 10,530 M = 10,533 SD = 0,366	Md = 10,830 M = 10,476 SD = 0,882	Md = 11,460 M = 11,397 SD = 0,475	Md = 11,435 M = 11,333 SD = 0,602	F(3,42) = 7,477 p < .001	SO vs. RMR** SO vs. RMR+AC* SO+AC vs. RMR** SO+AC vs. RMR+AC*
Phosphorus (mg/dl)	Md = 6,420 M = 6,392 SD = 1,010	Md = 6,210 M = 6,073 SD = 0,998	Md = 7,670 M = 8,209 SD = 1,707	Md = 7,165 M = 7,481 SD = 1,363	F(3,42) = 7,140 p < .001	SO vs. RMR** SO+AC vs. RMR**
BUN (mg/dl)	Md = 39,800 M = 40,433 SD = 6,866	Md = 45,200 M = 45,654 SD = 7,138	Md = 118,750 M = 147,167 SD = 69,824	Md = 87,125 M = 95,894 SD = 40,221	F(3,42) = 19,440 p < .001	SO vs. RMR** SO vs. RMR+AC* SO+AC vs. RMR** SO+AC vs. RMR+AC** RMR vs. RMR+AC*
Creatinine (mg/dl)	Md = 0,730 M = 0,739 SD = 0,069	Md = 0,700 M = 0,755 SD = 0,170	Md = 1,430 M = 1,691 SD = 0,799	Md = 1,085 M = 1,274 SD = 0,519	F(3,42) = 11,532 p < .001	SO vs. RMR** SO+AC vs. RMR**
Urinary Protein Excretion (g/day)	Md = 1,606 M = 1,517 SD = 0,310	Md = 1,729 M = 1,667 SD = 0,412	Md = 51,494 M = 45,603 SD = 20,440	Md = 22,598 M = 35,524 SD = 30,890	F(3,42) = 23,034 p < .001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC**
Creatinine Clearance (ml/min.)	Md = 1,600 M = 1,585 SD = 0,238	Md = 1,400 M = 1,462 SD = 0,301	Md = 0,700 M = 0,733 SD = 0,355	Md = 0,900 M = 0,950 SD = 0,366	F(3,42) = 20,214 p < .001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC**

SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid; Md: Median; M: Mean; SD: Standard Deviation; F: statistic from ANOVA; p: significant value from ANOVA test; (1): Bonferroni *post hoc* test; pairs of groups with statistically significant differences: *p < .05 and **p < .01.

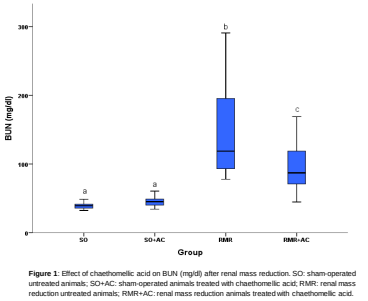

Figure 1: Effect of chaethomellic acid on BUN (mg/dl) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid.

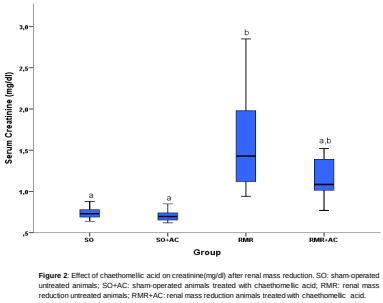

Figure 2: Effect of chaethomellic acid on creatinine(mg/dl) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid.

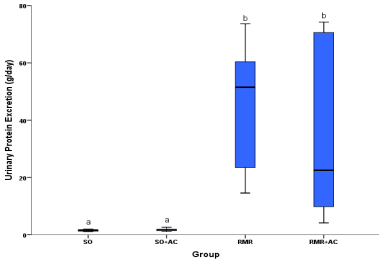

Figure 3: Effect of chaethomellic acid on urinary protein excretion (g/day) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid.

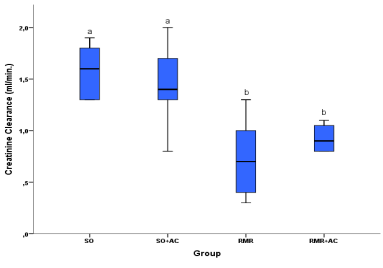

Figure 4: Effect of chaethomellic acid on creatinine clearance (ml/min.)) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid.

CONCLUSIONS

These results suggest that in a model of renal failure induced by RMR, six months of treatment with chaethomellic acid may have some beneficial effect on renal function.