



Universidade de Trás-os-Montes
e Alto Douro

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 significant 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	POSTHOC (1)
Urinary Flow (µl/min)	M=0.010 M=0.011 SD=0.002	M=0.009 M=0.009 SD=0.003	M=0.027 M=0.029 SD=0.008	M=0.023 M=0.025 SD=0.009	F(3,42)=34.729 p<0.001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC**
Sodium (mmol/l)	M=144.800 M=145.170 SD=1.831	M=143.980 M=142.229 SD=6.784	M=145.735 M=146.267 SD=4.218	M=147.245 M=146.388 SD=3.599	F(3,42)=2.497 p=0.73	
Potassium (mmol/l)	M=4.810 M=4.808 SD=0.355	M=4.710 M=4.511 SD=0.682	M=5.230 M=5.275 SD=0.472	M=4.820 M=4.849 SD=0.448	F(3,42)=4.064 p=0.05	SO+AC vs. RMR**
Chloride (mmol/l)	M=101.190 M=102.522 SD=4.268	M=101.340 M=99.715 SD=7.811	M=106.535 M=105.264 SD=5.278	M=108.870 M=107.284 SD=6.241	F(3,42)=3.186 p=0.03	SO+AC vs. RMR+AC*
Calcium (mg/dl)	M=10.530 M=10.533 SD=0.368	M=10.830 M=10.476 SD=0.882	M=11.397 M=11.267 SD=0.475	M=11.435 M=10.820 SD=0.602	F(3,42)=7.477 p<0.001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC*
Phosphorus (mg/dl)	M=6.420 M=6.392 SD=1.010	M=6.210 M=6.162 SD=0.998	M=7.870 M=8.220 SD=1.707	M=7.165 M=7.481 SD=1.383	F(3,42)=7.140 p=0.01	SO vs. RMR** SO+AC vs. RMR**
BUN (mg/dl)	M=39.800 M=40.433 SD=6.868	M=45.200 M=45.694 SD=7.138	M=116.790 M=117.397 SD=69.824	M=87.125 M=95.994 SD=40.221	F(3,42)=19.440 p<0.001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC** RMR vs. RMR+AC**
Creatinine (mg/dl)	M=0.730 M=0.739 SD=0.069	M=0.700 M=0.755 SD=0.170	M=1.430 M=1.691 SD=0.759	M=1.085 M=1.274 SD=0.519	F(3,42)=11.532 p<0.001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC**
Urinary Protein Excretion (µg/day)	M=1.606 M=1.517 SD=0.310	M=1.729 M=1.453 SD=0.412	M=51.494 M=45.603 SD=20.440	M=22.598 M=25.544 SD=30.890	F(3,42)=23.034 p<0.001	SO vs. RMR** SO vs. RMR+AC** SO+AC vs. RMR** SO+AC vs. RMR+AC**
Creatinine Clearance (ml/min)	M=1.600 M=1.586 SD=0.238	M=1.400 M=1.462 SD=0.301	M=0.700 M=0.733 SD=0.355	M=0.900 M=0.860 SD=0.366	F(3,42)=20.214 p<0.001	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. M: Mean; 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 difference: * $p < 0.05$ and ** $p < 0.01$.

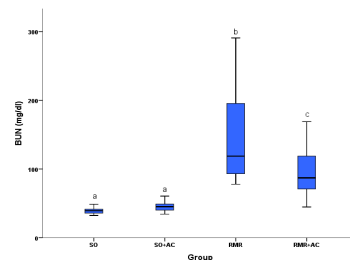


Figure 1: Effect of chaethomellic acid on BUN (mg/dl) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid.

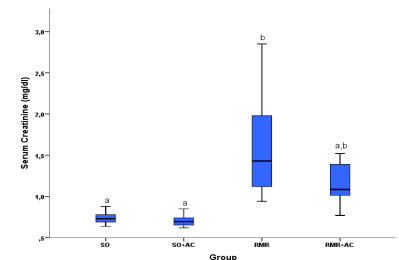


Figure 2: Effect of chaethomellic acid on creatinine (mg/dl) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic acid.

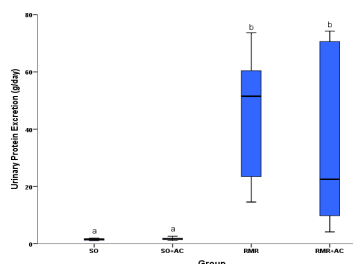


Figure 3: Effect of chaethomellic acid on urinary protein excretion (µg/day) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic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

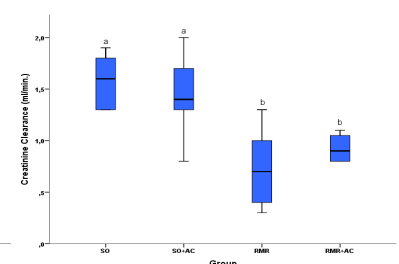


Figure 4: Effect of chaethomellic acid on creatinine clearance (ml/min) after renal mass reduction. SO: sham-operated untreated animals; SO+AC: sham-operated animals treated with chaethomellic acid; RMR: renal mass reduction untreated animals; RMR+AC: renal mass reduction animals treated with chaethomellic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