THE ORAL PURIFIED MICRONIZED FLAVONOID FRACTION EFFECT IN THE SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY

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Introduction and Objectives

Sepsis is characterized by a severe inflammatory response accompanied by depression in immunological function which causes multiple organ injury. Sepsis-associated acute kidney injury (AKI) pathophysiology changes includes renal vasoconstriction, ischemia and acute tubular apoptosis. The concept of renal vasoconstriction and kidney ischemia as a key pathogenic factor is certainly valid for sepsis models. Sepsis-associated AKI may result from global renal hypoperfusion, which is locally mediated by the upregulation of pro-inflammatory cytokines (TNF-α and IL-6), with subsequent tubular cell apoptosis also in distan organs. The purified micronized flavonoid fraction improves venous tone and reduces capillary hyperpermeability by protecting the microcirculation from inflammatory processes.

This study evaluated the effect of the purified micronized flavonoid fraction (Diosmin/Hesperidin) on sepsis induced AKI in rats.

Methods

- Animals: adult, male, Wistar rats weighing 300 g divided in:
  - **SHAM** - control without cecal ligature and puncture (CLP);
  - **Sepsis** - sepsis was induced by CLP;
  - **Sepsis+Diosmin** – Diosmin/Hesperidin 3 mg/kg, 30 min before CLP.
- Physiological Parameters: body temperature, mean arterial pressure.
- Renal Function: creatinine clearance.
- Oxidative Metabolites: peroxides urinary and thiobarbituric acid reactive substances (TBARS).
- Inflammatory Response: kidney, lung and intestinal tract levels of TNF-α and IL-6 (ELISA).
- Renal Histological Analysis.
- Statistical Analysis: differences between groups were analyzed by one way analyses of variance ANOVA and post hoc Bonferroni test. Results are presented as mean±SEM and $p<0.05$ was considered statistically significant.

Results

CLP induced a polymicrobial bacteremia and sepsis by decreased body temperature and mean arterial pressure (**Table 1**). Sepsis animals demonstrated creatinine clearance reduction (**Tabela 2**), accompanied by a prominent urinary peroxides index (**Table 3**). These parameters were significantly changed in the Diosmin/Hesperidin treatment group.

Groups	Body Temperature (°C)	Medium Arterial Pressure (mmHg)
SHAM	36.4±0.15	88.3±3.21
SEPSIS	34.3±1.30^{A}	60.2±17.7^{A}
SEPSIS+DIOSMIN	35.7±0.87^{AB}	91.8±5.67^{B}

Data reported mean±SEM. $^{A}p<0.05$ vs SHAM, $^{B}p<0.05$ vs Sepsis

Table 2: Renal function.

Groups	Urine Output (ml/min)	Urinary Creatinine (mg/dl)	Serum Creatinine (mg/dl)	Creatinine Clearance (ml/min 100g)
SHAM	0.009±0.002	75.76±12.76	0.39±0.04	0.60±0.11
SEPSIS	0.011±0.004	39.65±14.39^{A}	0.72±0.09^{A}	0.25±0.02^{A}
SEPSIS+DIOSMIN	0.018±0.009^{A}	43.33±11.06^{A}	0.41±0.05^{B}	0.34±0.03^{AB}

Data reported mean±SEM. $^{A}p<0.01$ vs SHAM, $^{B}p<0.05$ vs Sepsis

Table 3: Oxidative Metabolites.

Groups	Urinary Peroxides (nmol/mg urinary creatinine)	Urinary TBARS (nmol/mg urinary creatinine)
SHAM	3.48±0.66	4.38±2.19
SEPSIS	13.97±5.14^{A}	13.06±3.40^{A}
SEPSIS+DIOSMIN	4.75±2.89^{B}	7.44±3.11^{AB}

Data reported mean±SEM. $^{A}p<0.001$ vs SHAM, $^{B}p<0.05$ vs Sepsis

A similar quantitative inflammatory response in distant organs and in the kidneys was observed in CLP animals (**Figure 1**). Renal histology analysis demonstrated loss of brush border with severe dilation on the tubular lumen after sepsis induced CLP model (**Figure 2**).

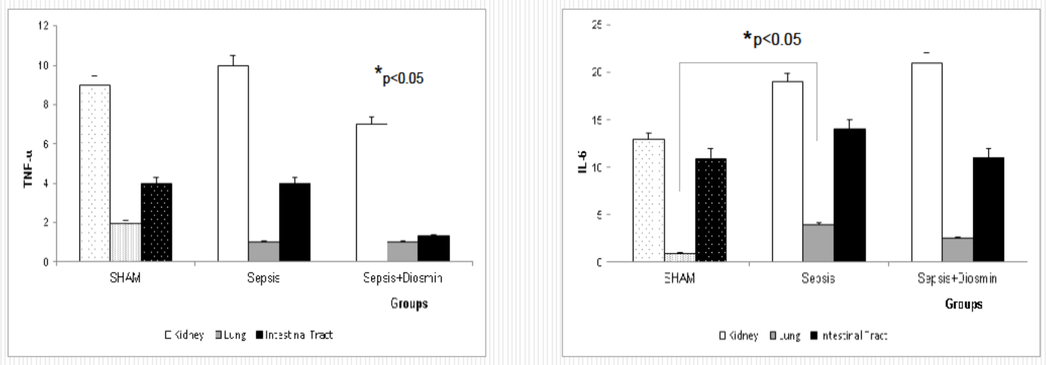

Figure 1: Inflammatory response: TNF-α and IL-6.

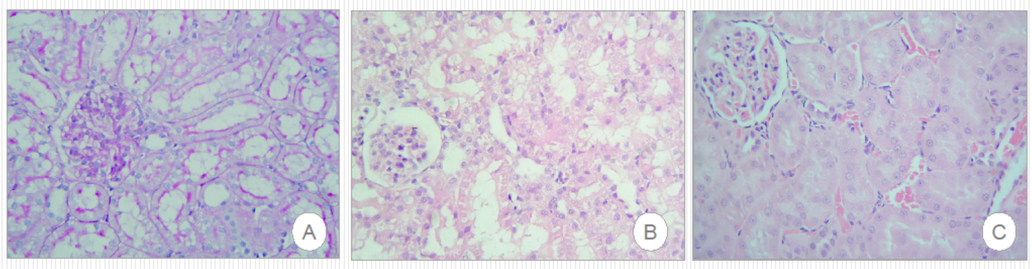

Figure 2: Renal histological analysis. (**A**) SHAM, (**B**) Sepsis, (**C**) Sepsis+Diosmin

Conclusions

Sepsis is an injury repair stereotyped response across remote organs. Distant organ inflammation can be considered a significantly mediator of sepsis-associated AKI. These data provide a new insight about Diosmin/Hesperidin attenuating effect in the sepsis induced AKI.

References

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