

## **NOBILETIN, A FLAVONE FROM SHEKWASHA (CITRUS DEPRESSA), ALLEVIATES HYPERTENSIVE BLADDER RESPONSE IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS RATS.**

### Hypothesis / aims of study

Phytotherapeutic agents are very popular in many European countries as herbal remedies represent up to 80% of all drugs prescribed for these disorders[1]. Nobiletin, is a polymethoxy flavonoid abundantly present in citrus fruits, including shekwasha (*Citrus depressa*) produced in southern parts of Japan such as Okinawa. Previously, we reported that nobiletin has binding potential to muscarinic receptor and alleviates acetic acid-induced hypertensive bladder response in rats. This study aimed to clarify the effect of nobiletin on urodynamic functions in anesthetized cystitis rat cystometry. Furthermore, to understand the mechanism of effect of nobiletin on urodynamic functions, we performed in vitro organ bath study and measured intracellular cAMP concentration on rat bladder strips.

### Study design, materials and methods

The effect of single oral administration of nobiletin mixture (50 mg/kg) was examined on urodynamic parameters in cystometrograms of anesthetized cystitis rats induced by cyclophosphamide. In organ bath study, rat urine bladder smooth muscle strips were placed in organ baths containing 10 mL of an aerated Krebs-Henseleit solution, and contractions were recorded using isometric force displacement transducers. Following the acquisition of control 80 mM KCl response, acetylcholine (ACh) was added to the bath at 100  $\mu$ M. Then, to investigate the effect of nobiletin on ACh-induced contraction, it was added at 1 mM and harvested bladder strips for measuring intracellular cAMP.

### Results

Single oral administration of nobiletin in CYP-induced cystitis rat cystometry caused an increase in the micturition interval and voided volume and a significant decrease of micturition frequency during the intravesical infusion of saline. The nobiletin had little effect on the threshold pressure and basal pressure, but maximum micturition pressure was significantly decreased (fig. 1). Nobiletin significantly inhibited ACh-induced contraction on the rat bladder strips and significantly increased intracellular cAMP concentration (fig. 2).

### Interpretation of results

Single oral administration of nobiletin alleviated significantly urodynamic symptoms in hyperactive rat bladder by prolonging the micturition interval and decreasing micturition frequency. Although the precise mechanism which nobiletin improved a hyperactive bladder response in CYP-induced cystitis rats remains to be clarified, the potency of increasing intracellular cAMP in the bladder smooth muscles may be partly contribute to the beneficial effect.

### Concluding message

Nobiletin improved significantly urodynamic symptoms in hyperactive rat bladders by decreasing the micturition frequency. Thus, the current results may support the clinical efficacy of nobiletin mixture in the treatment of lower urinary tract symptoms accompanying overactive bladder.

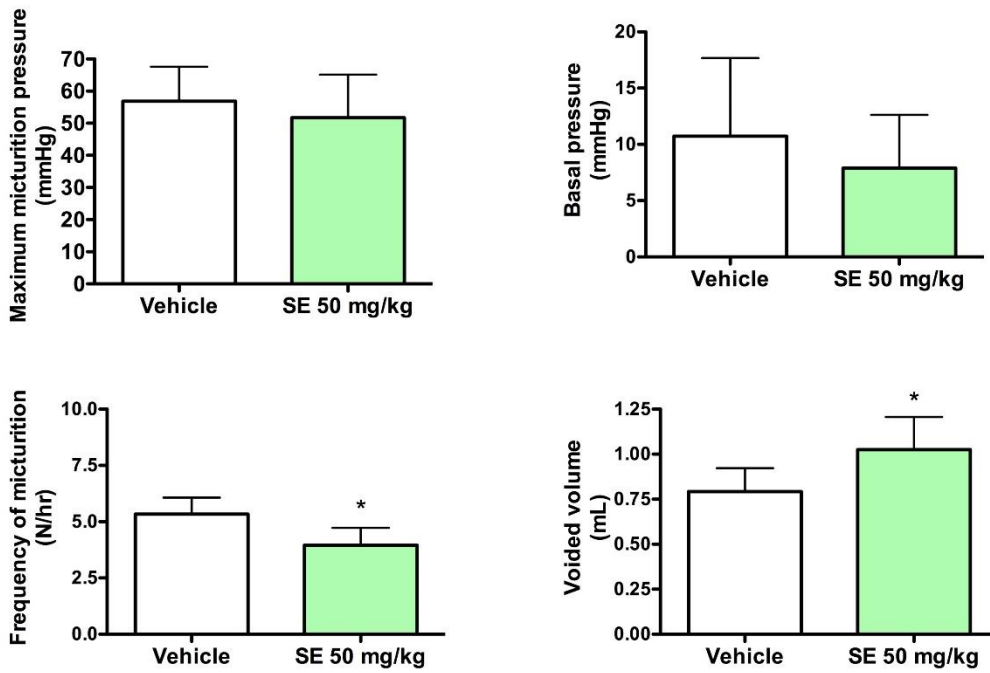


Fig. 1 Effect of oral administration of nobiletin on urodynamic parameters in CYP-induced cystitis rats. Each values represents mean  $\pm$  S.D. of 6 experiments. Astarisks show significant differences from vehicle, \* $P < 0.05$ .

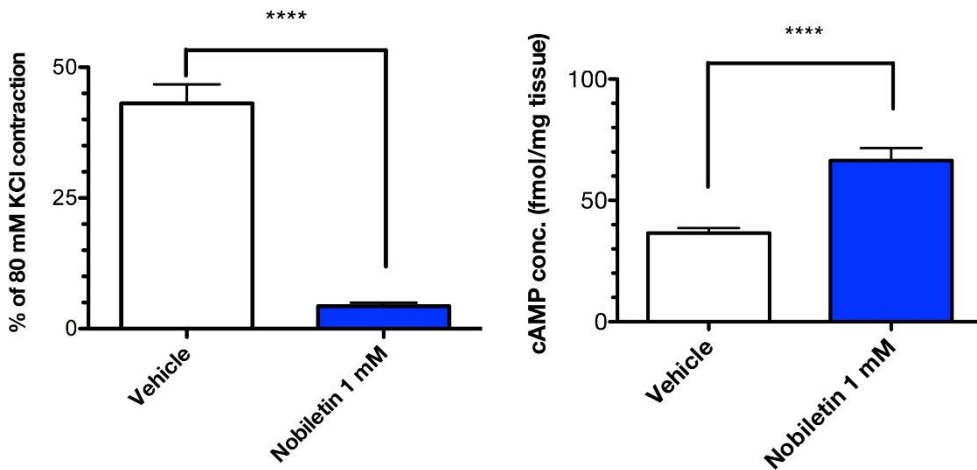


Fig.2 Effect of nobiletin on ACh-induced contraction and intracellular cAMP concentration in rat bladder strips. Each values represents mean  $\pm$  S.D. of 8 experiments. Astarisks show significant differences from vehicle, \*\*\*\* $P < 0.0001$ .

#### References

1. Br J Urol, 78: 325 (1996)

#### Disclosures

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