NOBILETIN, A FLAVONE FROM SHEKWASHA (CITRUS DEPRESSA), ALLEVIATES ACETIC ACID-INDUCED HYPERTENSIVE BLADDER RESPONSE IN RATS

Hypothesis / aims of study
Phytotherapeutic agents are very popular in many European countries as herbal remedies and represent up to 80% of all drugs prescribed for these disorders.1 Debruyne et al2 reported that Permixon® (lipid-sterolic extract of SPE) and alpha1-blocker are equivalent in the medical treatment of lower urinary tract symptoms in men with BPH over 12 months. Nobiletin, a polymethoxy flavonoid abundantly present in Citrus fruits, including shekwasha (Citrus depressa) produced in southern parts of Japan such as Okinawa. Current studies have shown that nobiletin exhibits anti-inflammatory, antiallergenic, antithromosclerotic and antitumor activities. This study aimed to clarify the effect of a shekwasha extract containing nobiletin and tangeretin (called as nobiletin mixture), on urodynamic functions in anesthetized rat cystometry. Furthermore, the binding activity of nobiletin on muscarinic, alpha1-adrenergic and purinergic receptors was examined.

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 rats induced by intravesical infusion of 0.1% acetic acid. The autonomic (muscarinic, alpha1-adrenergic and purinergic) receptor binding activity of nobiletin mixture in the rat tissue was examined by radioligand binding assay using [3H]pirenzepine, [3H]prazosin and [3H]alpha,beta-methyleneATP as selective radioligands of muscarinic, alpha1-adrenergic and purinergic receptors.

Results
Single oral administration of nobiletin mixture (50 mg/kg) in 0.1% acetic acid-infused rat cystometry caused an increase in the micturition interval and voided volume and a significant decrease of micturition frequency during the intravesical infusion of 0.1% acetic acid. The nobiletin mixture had little effect on the threshold pressure and basal pressure, but maximum micturition pressure was significantly increased. Nobiletin inhibited specific [3H]pirenzepine binding in the rat brain in a concentration dependent manner with Ki values of 12.1 µM. Nobiletin had little effect on the alpha1-adrenergic and purinergic receptor binding activity in the rat tissue, evaluated by radioligand binding assays using [3H]prazosin and [3H]alpha,beta-methyleneATP.

Each values represents mean ± S.D. of 17 experiments. Asterisks show significant differences from vehicle, *P<0.05, **P<0.001.

Fig. 1 Effect of oral administration of nobiletin mixture on urodynamic parameters in rats with 0.1% acetic acid-induced frequent urination.
Interpretation of results
Single oral administration of nobiletin mixture alleviated significantly urodynamic symptoms in hyperactive rat bladder by prolonging the micturition interval and decreasing micturition frequency. Although the precise mechanism which nobiletin mixture improved a hyperactive bladder response in acetic acid-infused rats remains to be clarified, the potency of binding to muscarinic receptor 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.

References

Disclosures
Funding: Non Clinical Trial: No Subjects: ANIMAL Species: Rat Ethics Committee: the Institutional Animal Care and Use Committee of the University of Shizuoka