学 位 論 文 の 要 旨

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学 位 論 文 名　A Phytosterol Enriched Refined Extract of Brassica Campestris L. Pollen Significantly Improves Benign Prostatic Hyperplasia (BPH) in a Rat Model as Compared to the Classical TCM Pollen Preparation Qianlie Kang Pule'an Tablets

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論 文 内 容 の 要 旨

INTRODUCTION

Benign prostate hyperplasia (BPH) is one of the most common diseases among elderly men in East Asia and exhibits gradually increasing incidence rates. In Qinghai Province, PR China, the *Brassica campestris L.* pollen preparation Qianlie Kang Pule'an Tablet (QKPT) is traditionally used for BPH therapy. QKPT is an adaptogenic traditional Chinese medicine (TCM) preparation for symptoms of weakened renal qi, commonly used in the treatment of chronic prostatitis, prostatic hyperplasia, incontinence, as well as for soreness and weakness of waist and knees. However, in QKPT the content of supposedly active phytosterols is relatively low, necessitating high doses for successful therapy. Therefore, a phytosterol enriched refined extract of *B. campestris* pollen (PE) was developed.

MATERIALS AND METHODS

The preparation method of PE is that 10kg pollen was broken down and extracted

with 95% ethanol twice, and two liquid extracts were mixed and evaporated into dry, and then yield 2.0 kg of the examined pollen extract PE. The over-all contents of phytosterolsin and β-sitosterol, which are considered as the most active compounds, were determined by the classical TCM pollen preparation. The over-all contents of phytosterolsin in QKPT and in PE were 2.59% and 4.54% respectively, and the contents of β-sitosterol were 0.101% and 0.057% respectively. In the present animal model, androgen-driven BPH was triggered by administering super-physiological testosterone-doses to castrated male rats.

In castrated rats, this main source of endogenous dihydrotestosterone (DHT) is incapacitated thus promoting prostate atrophy. Subsequent administration of exogenous testosterone lessens the effects of castration, reactivating prostate growth, and after injection of super-physiological doses leads to hyperplasia. The effect of PE on BPH rat model was compared with QKPT. Six groups of rats (n = 8 each), namely sham-operated distilled water control, castrated distilled water control, castrated QKPT 2.0 g/kg, castrated PE 0.1 g/kg, castrated PE 0.2 g/kg, and castrated PE 0.4 g/kg, were intragastrically treated with the respective daily doses. Testosterone propionate (0.3 mg/day) was administered to all castrated rats, while the sham-operated group received placebo injections. After 30 days, the animals were sacrificed and prostates as well as seminal vesicles excised and weighted in order to calculate prostate volume index (PVI) as well as prostate index (PI) and seminal vesicle index (SVI), defined as organ weight in g per 100 g body weight.

RESULTS AND DISCUSSION

Compared with sham-operated controls, PI ($p < 0.01$), PVI ($p < 0.01$), and SVI ($p < 0.01$) were all significantly increased in all castrated, testosterone treated rats. After treatment with PE at 0.4 and 0.2 g/kg or QKPT at 2.0 g/kg per day, both indices were significantly reduced ($p < 0.01$) as compared to the castrated distilled water control. For PE at 0.1 g/kg per day only PI was significantly reduced ($p < 0.05$). At the highest PE concentration of 0.4 g/kg per day both PI and SVI were also significantly reduced when compared to the QKPT group ($p < 0.05$).

In this study, a pathological classification standard for the severity of the hyperplastic state of the prostates of test animals was designed. Most of the animals in the castrated distilled water control group suffered from serious pathological changes in

their prostates. However, these symptoms were significantly reduced by treatment with PE at 0.4 and 0.2 g/kg ($p < 0.01$, $p < 0.05$). In the castrated distilled water control group, the prostatic epithelial cells proliferated to significantly higher levels than in the sham-operated distilled water control group, and the prostatic glandular cavities were also markedly enlarged. In the three PE groups and in the QKPT group both epithelial cell proliferation and glandular cavity enlargement were significantly reduced. Both maximal glandular cavity diameters and glandular epithelium height in the distilled water control group were significantly larger than those in the sham-operated distilled water control group ($p < 0.01$). In comparison with the distilled water control group, the glandular cavity diameters in the PE 0.4 and 0.2 g/kg groups as well as in the QKPT 2.0 g/kg group were significantly reduced ($p < 0.01$). A similarly significant reduction of glandular epithelium height in the PE 0.4 g/kg group was also observed ($p < 0.05$). In addition, the effects of high-dose PE (0.4 g/kg) on pathological changes of hyperplastic prostates were somewhat favourable in comparison with those of QKPT 2.0 g/kg, which contains an equivalent amount of pollen.

CONCLUSION

In conclusion, both PE and QKPT demonstrated curative effects against BPH in the applied animal model. In its highest dose at 0.4 g/kg per day, PE was clearly superior to QKPT.

論文審査及び最終試験又は学力の確認の結果の要旨

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学位論文名	A Phytosterol Enriched Refined Extract of *Brassica campestris L.* Pollen Significantly Improves Benign Prostatic Hyperplasia (BPH) in a Rat Model as Compared to the Classical TCM Pollen Preparation Qianlie Kang Pule'an Tablets	
学位論文審査委員	主 査	椎名 浩昭
	副 査	和田 孝一郎
	副 査	杉本 利嗣

論文審査の結果の要旨

男性の排尿障害の原因として、前立腺肥大症が占める割合は年齢とともに増加する。前立腺肥大症の治療としてαブロッカーや5α還元酵素阻害剤などが使用されるが、中国ではTraditional Chinese Medicine (TCM)として菜の花 (*Brassica campestris*) の花粉団子製剤 (QKPT) が前立腺肥大症の治療に用いられる。申請者らは、この製剤に着目し花粉を粉砕後、95%エタノール抽出物 (PE) とした改良製剤を作成した。なお、QKPTの活性物質はβ-sitosterolを含むphytosterolとされるが、今回用いたPEにも同じ組成のβ-sitosterolを含むphytosterolが高速液体クロマトグラフィで同定された。まず、去勢ラットにtestosterone propionateを0.3 mg/day、30日間連続投与し前立腺肥大症モデルを作成し、PEとQKPTの効果を検討した。PEはそれぞれ3種類の濃度 (0.1 g/kg/日、0.2 g/kg/日、0.4 g/kg/日) とし、QKPTは濃度2.0 g/kg/日を用いた。それぞれの薬剤を30日間経口投与した後、ラットを安楽死させ、前立腺指数、前立腺容積指数、精嚢指数および前立腺の病理学的変化 (前立腺管腔径と腺上皮高) を指標としてPEとQKPTの抗アンドロゲン作用を評価した。未治療群前立腺肥大症ラットに比較し、PEあるいはQKPT投与群では前立腺指数、前立腺容積指数あるいは精嚢指数の有意な低下を認めた。さらに病理学的所見でもPEあるいはQKPT投与群では前立腺管腔径あるいは腺上皮高の低下が観察された。一方、QKPT投与群の前立腺指数、前立腺容積指数、精嚢指数および前立腺管腔径と腺上皮高はPE濃度0.2 g/kg/日とほぼ相同であったが、PE濃度0.4 g/kg/日と比較するといずれも有意に高かった。QKPT 2gからPE 0.4gが抽出されることを考慮すると、PEの抗アンドロゲン作用の力価はQKPTよりも高いことが示唆された。

最終試験又は学力の確認の結果の要旨

申請者は中国で前立腺肥大症治療薬として使用される花粉団子製剤 (QKPT) に着目し、その改良製剤としてエタノール抽出物(PE)を作成し、その抗アンドロゲン作用をラット前立腺肥大症モデルで検証した。PEの抗アンドロゲン作用の力価がQKPTよりも高いことを証明し、またPEが前立腺肥大症のみならず前立腺癌に対する治療戦略にもなりうる可能性も示唆した。関連知識も豊富で学位授与に値すると判断した。

(主査：椎名 浩昭)

申請者は、Traditional Chinese Medicine において前立腺肥大の治療に使用されている「菜の花・花粉由来の打錠製剤」の問題点に着目し、エタノール抽出による有効成分の濃縮を行った。β-sitosterolなどの有効成分が濃縮された抽出物は、ラット前立腺肥大モデルにおいて打錠製剤よりもすぐれた抑制効果を示し、薬効発現や吸収性といった薬理学的有用性が高いことが示唆された。公開審査での質疑応答も的確であり、関連知識も豊富であることなどから学位授与に値すると判断した。

(副査：和田 孝一郎)

申請者は中国で前立腺肥大症の治療に用いられているQKPTの改良製剤の開発を目的として粉砕した花粉からPEを作成し、前立腺肥大症モデルラットに対する作用を検討した。PEはQKPTより前立腺肥大抑制効果ならびに抗アンドロゲン作用が強いことを立証した。臨床的にも意義ある研究成果であり、関連知識も豊富であることより、学位授与に値すると判断した。

(副査：杉本 利嗣)

(備考) 要旨は、それぞれ４００字程度とする。