

Original Article

Int Neurorol J 2014;18:179-186

<http://dx.doi.org/10.5213/inj.2014.18.4.179>

pISSN 2093-4777 · eISSN 2093-6931



Influence of *Panax ginseng* on Alpha-Adrenergic Receptor of Benign Prostatic Hyperplasia

Su Kang Kim¹, Joo-Ho Chung¹, Byung-Cheol Lee², Sang Won Lee³, Kang Hyo Lee⁴, Young Ock Kim³

¹Kohwang Medical Research Institute, Kyung Hee University School of Medicine, Seoul, Korea

²Department of Internal Medicine, College of Oriental Medicine, Kyung Hee University, Seoul, Korea

³Herbal Crop Utilization Research Team, Department of Medicinal Crop Research Institute, Eumseong, Korea

⁴Mushroom Research Division, National Institute of Horticulture & Herbal Science, Rural Administration, Eumseong, Korea



Purpose: Benign prostatic hyperplasia (BPH) is the most common prostate problem in older men. The present study aimed to investigate the inhibitory effect of *Panax ginseng* C.A. Meyer (*P. ginseng*) on a rat model of testosterone-induced BPH.

Methods: The rats were divided into 3 groups (each group, n = 10): control, testosterone-induced BPH (20 mg/kg, subcutaneous injection), and *P. ginseng* (200 mg/kg, orally) groups. After 4 weeks, all animals were sacrificed to examine the blood biochemical profiles, prostate volume, weight, histopathological changes, alpha-1D adrenergic receptor (Adra1d) mRNA expression, and epidermal growth factor receptor (EGFR) and B-cell CLL/lymphoma 2 (BCL2) protein expression.

Results: The group treated with *P. ginseng* showed significantly lesser prostate size and weight than the testosterone-induced BPH group. In addition, *P. ginseng* decreased the mRNA expression of Adra1d as well as the expression of EGFR and BCL2 in prostate tissue.

Conclusions: These results suggest that *P. ginseng* may inhibit the alpha-1-adrenergic receptor to suppress the development of BPH.


Keywords: Prostatic Hyperplasia; Receptors, Adrenergic, alpha-1; Panax; Testosterone

- **Grant Support:** This study was supported by grants from the "Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ009558)" Rural Development Administration, Republic of Korea.
- **Research Ethics:** All experiments were carried out according to the protocols approved by the Animal Care Committee of the Animal Center at Kyung Hee University and in accordance with guidelines from the Korean National Health Institute of Health Animal Facility [KHUASP(SE)-13-024].
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common urological disease in aged men. It is characterized by benign enlargement of the prostate. The male urethra runs through the prostate, and therefore an enlarged prostate may constrict the urethra and cause lower urinary tract symptoms (LUTS), including difficult

and weak urination, frequent voiding, nocturia, dysuria, and bladder obstruction [1]. These symptoms can negatively affect the quality of life of BPH patients. BPH generally does not occur before the age of 30, but it often develops between the ages of 30 and 80. By 80 years of age, approximately 90% of men would develop BPH [2]. Late treatment of prostatic hyperplasia leads to several issues, such as acute urinary retention, renal insufficien-

Corresponding author: Young Ock Kim  <http://orcid.org/0000-0001-6661-5153>
Herbal Crop Utilization Research Team, Department of Medicinal Crop Research Institute, Rural Administration, 92 Bisan-ro, Soi-myeon, Eumseong 369-873, Korea

E-mail: kyo9128@korea.kr / Tel: +82-43-871-5585 / Fax: +82-43-871-5589

Submitted: September 29, 2014 / **Accepted after revision:** November 15, 2014



This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

cy, urinary tract infection, gross hematuria, bladder stones, and kidney failure [3-5].

Although the pathogenesis of BPH is not exact, previous studies have reported that sex hormones, including androgen, testosterone, and dihydrotestosterone (DHT), contribute to BPH development. For BPH patients, two main treatment options exist: 5- α reductase inhibitors and alpha-1-adrenergic receptor antagonists [6].

DHT, a highly active metabolite of testosterone that is synthesized by the prostate 5- α reductase enzyme, is known to be a major contributor to BPH pathology [7]. Hence, 5- α reductase inhibitors such as finasteride and dutasteride have been used to treat BPH [8]. Alpha-1-adrenergic receptors exist in the prostate, urethra, bladder, vascular tissues, and central nervous system [9]. Alpha-1-adrenergic receptors are found in approximately 69.3% of the normal prostate tissue. In contrast, they are present in up to 85% of prostate tissue in BPH [9]. Alpha-1-adrenergic receptor antagonists, such as alfuzosin, doxazosin, tamsulosin, and terazosin, have been used to reduce the symptoms of BPH [10]. However, these drugs can produce undesirable side effects including erectile dysfunction, loss of libido, dizziness, severe myopathy, and chest pain [11].

Recent studies have suggested that commonly used herbal agents may effectively treat BPH or inhibit the development of BPH. Previous reports have shown that *Aframomum melegueta* extract ameliorates BPH in Wistar rats [12]. The extract consists of alkaloids, flavonoids, saponins, tannins, cardiac glycosides, terpenoids, and steroids. *Melandrium firmum* extract was also found to be effective against BPH development; it was found to contain some saponins, saponin, flavonoids, and triterpenoids [13]. Moreover, Bae et al. [14] reported that the water extract of Korean red ginseng and 20(S)-Rg3 represses androgen receptor activity. Saponins and ginsenosides are the major constituents of *P. ginseng* extract [15].

Ginseng is the commonly known name of the root of *P. ginseng*, which is very widely used in traditional herbal medicine in East Asia. *P. ginseng* has been evaluated for various protective effects against degenerative and aging-related conditions, such as neurodegenerative diseases [16], diabetic nephropathy [17], osteoporosis [18], ischemia, and oxidative stress [19]. However, the efficacy of *P. ginseng* against BPH has not yet been studied. Hence, in this study, we evaluated the effect of *P. ginseng* on a testosterone-induced BPH rat model and investigated the underlying molecular mechanism.

MATERIALS AND METHODS

Preparation of the *Panax ginseng* C.A. Meyer (*P. ginseng*)

P. ginseng is Korean ginseng. The sample was collected at the Department of Medicinal Crop Research (Eumsung, Korea) in September 2010. To obtain the water extract of ginseng, 100 g of ginseng root was added to 600 mL of distilled water, and extraction was performed by heating at 95°C. It was then filtered through muslin cloth and lyophilized. The resulting powder (yield, 32 g) was dissolved in distilled water and sequentially passed through 0.22- μ m filters for sterilization.

Animals

Seven-week-old male Wistar rats (Central Lab Animal Inc., Seoul, Korea) with an average body weight of 250 ± 10 g were used in this study. The animal room was maintained at $22 \pm 2^\circ\text{C}$ and at 40%–70% relative humidity with a 12-hour light/dark cycle. All experiments were carried out according to the protocols approved by the Animal Care Committee of the Animal Center at Kyung Hee University and in accordance with guidelines from the Korean National Health Institute of Health Animal Facility [KHUASP(SE)-13-024].

Induction of BPH and Treatments

The testes of the rats in the BPH and the *P. ginseng* groups were removed to exclude the influence of intrinsic testosterone. The spermatic cord and blood vessels were ligated with Silkam sutures 3/8–16 mm (B.Braun Surgical SA, Rubi, Spain) and resected. BPH was induced by subcutaneous injection of testosterone (20 mg/kg; Wako chemicals, Tokyo, Japan) for 4 weeks after castration. Rats were divided into 3 groups (each group, $n = 10$): (1) control group, (2) testosterone-induced (subcutaneous) BPH group, and (3) *P. ginseng* treated group (200 mg/kg oral administration; Sigma-Aldrich, St. Louis, MO, USA). Based on previous studies, we treated rats with 200 mg/kg of *P. ginseng* [20,21]. All materials were administered to the animals once daily for 4 weeks, and body weight was measured weekly. After 4 weeks, all animals were fasted overnight. Blood was collected in ethylenediaminetetraacetic acid tubes, placed on ice, and the serum was immediately separated and stored at -20°C . After the animals were sacrificed, the tissue of prostate was stored in formaldehyde solution for light microscopic observation. The rest of the prostate was stored at -70°C for subsequent analysis.

Blood Collection and Biochemical Analysis

At the end of the experiment, the food was removed and experiments were performed between 9 AM and 12 PM. Blood samples were obtained from the heart of the rats at the end of the experiment. Blood samples were rapidly centrifuged at $3,000 \times g$ for 15 minutes at 4°C , and serum was obtained and stored at -70°C before analysis. Glucose, total protein, glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) levels were analyzed by Greenlab (Seoul, Korea).

Histopathological Examination

Fixed prostate tissue embedded in paraffin wax were cut into $5\text{-}\mu\text{m}$ -thick sections and stained with hematoxylin and eosin. The sections were mounted and cover slipped using mounting solution and then examined under a microscope. Prostate epithelial thickness was measured.

Immunohistochemistry

Immunostaining was performed on $4\text{-}\mu\text{m}$ -thick sections after deparaffinization. Microwave antigen retrieval was performed in citrate buffer, pH 6.0, for 10 minutes prior to peroxide quenching with $3\% \text{H}_2\text{O}_2$ in phosphate buffered saline (PBS) for 10 minutes. Sections were then washed in water and preblocked with normal goat or rabbit serum for 10 minutes. In the primary antibody reaction, slides were incubated with anti-epidermal growth factor receptor (EGFR) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) in a 1:200 dilution and then anti-BCL2 (Santa Cruz Biotechnology) in a 1:200 dilution overnight at 4°C . The sections were then incubated with biotinylated secondary antibodies (1:1,000) for 1 hour. Following a washing step with PBS, streptavidin-horseradish peroxidase was applied. Finally, the sections were rinsed in PBS and developed with diaminobenzidine tetrahydrochloride substrate for 10 minutes. At least three random fields of each section were examined at $\times 100$.

RNA Extraction and Reverse Transcriptase-Polymerase Chain Reaction

Total RNA was isolated from the prostate tissues of each mouse using Trizol (Invitrogen, Carlsbad, CA, USA), according to the manufacturer's instructions. An aliquot of total RNA was reverse transcribed and amplified using MMuLV reverse transcriptase and Taq DNA polymerase (Promega, Madison, WI, USA). Primers for reverse transcription (reverse transcriptase-polymerase chain reaction, RT-PCR) analysis were designed. The sequences of the designed primers were as follows: alpha-

1D adrenergic receptor (Adra1d), sense: $5' \text{-TGGTATCTGTGGGACCGCTA-3'}$ and antisense: $5' \text{-CACGATCACTGC-CATGGGTA-3'}$.

Statistical Analyses

All the values are expressed as the mean \pm standard error. Significant differences between the groups were statistically analyzed using one-way analysis of variance (ANOVA), followed by a nonparametric *post hoc* Tukey test. All P-values are two-tailed, and significance was set at $P < 0.05$. All statistical analyses were performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Effect of *P. ginseng* on Weight Change

Body weight change is shown in Table 1. Final body weight was measured after 30 days, and each group showed an increase compared to their initial body weight (control group, 69.4%; BPH group, 70.2%; *P. ginseng* group, 69.4%). However, differences in weight change between the groups were not significant ($P > 0.05$).

Effect of *P. ginseng* on Glucose, Total Protein, GOT, and GPT Levels in Serum

The BPH group displayed lower glucose levels than the control group (Table 2). The plasma glucose levels of the *P. ginseng* treatment group were affected, but the differences were not statistically significant ($P > 0.05$). GOT and GPT levels in serum were not significantly different among groups. *P. ginseng* did not promote the activity of the serum toxicity marker enzymes GOT and GPT indicating that each group of rats had normally functioning livers. Total protein levels in the serum of the BPH group were slightly elevated compared to those of the control,

Table 1. Body weight gains in each group

Group	Initial weight (g)	Final weight (g)	Total body weight gains for 30 days (g)
Control ^{a)}	250	360.00 \pm 9.58	110.00 \pm 9.58
BPH ^{b)}	250	356.00 \pm 8.06	106.00 \pm 8.06
<i>P. ginseng</i> ^{c)}	250	360.00 \pm 12.11	110.00 \pm 12.11

Values are presented as mean \pm standard error (n = 10).

BPH, benign prostatic hyperplasia; *P. ginseng*, *Panax ginseng*.

^{a)}Not treated group. ^{b)}BPH, testosterone injection group. ^{c)}Testosterone injection and *P. ginseng* (200 mg/kg) group.

Table 2. Glucose, total protein, GOT, and GPT serum level in each group

Group	Glucose (mg/dL)	Total protein (g/dL)	GOT (U/L)	GPT (U/L)
Control ^{a)}	131.56 ± 7.21	5.78 ± 0.06	91.67 ± 5.83	28.45 ± 1.40
BPH ^{b)}	113.20 ± 4.11	5.91 ± 0.06	100.50 ± 9.12	28.20 ± 1.37
<i>P. ginseng</i> ^{c)}	138.50 ± 6.49	5.67 ± 0.02	89.88 ± 5.37	29.50 ± 1.48

Values are presented as mean ± standard error (n = 10).

GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BPH, benign prostatic hyperplasia; *P. ginseng*, *Panax ginseng*.

^{a)}Not treated group. ^{b)}BPH, testosterone injection group. ^{c)}Testosterone injection and *P. ginseng* (200 mg/kg) group.

Table 3. Prostate weight, prostate volume, and prostate weight ratio in each group

Group	Prostate weight (g)	Prostate volume (cm ³)	Prostate weight ratio (mg/100 g of BW)
Control ^{a)}	1.01 ± 0.03	0.97 ± 0.11	0.28 ± 0.01
BPH ^{b)}	1.30 ± 0.05***	1.75 ± 0.15***	0.38 ± 0.03***
<i>P. ginseng</i> ^{c)}	0.97 ± 0.06***	0.93 ± 0.14***	0.27 ± 0.02***

Values are presented as mean ± standard error (n = 10).

BW, body weight; BPH, benign prostatic hyperplasia; *P. ginseng*, *Panax ginseng*.

^{a)}Not treated group. ^{b)}BPH, testosterone injection group. ^{c)}Testosterone injection and *P. ginseng* (200 mg/kg) group.

***P < 0.001 compared with control group. ***P < 0.001 compared with BPH group.

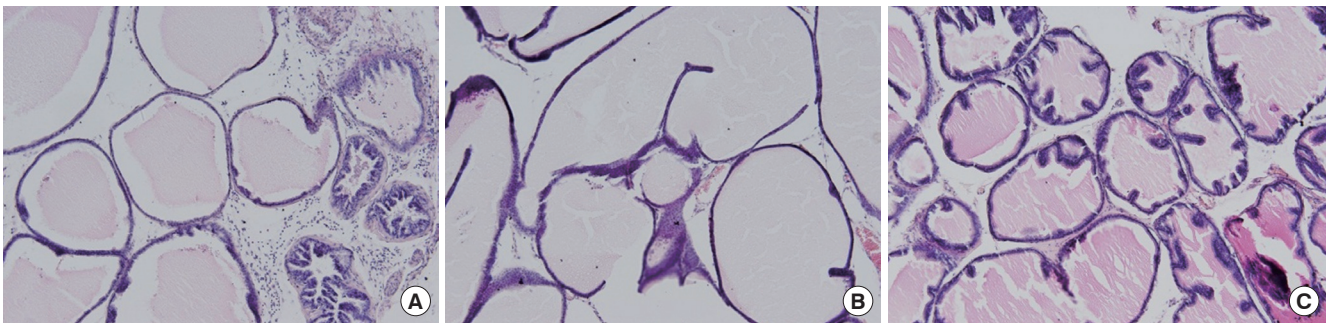


Fig. 1. H&E stains of prostate tissue from the rats (× 100). (A) Not treated group, (B) BPH, testosterone injection group, (C) testosterone injection and *P. ginseng* (200 mg/kg) group. BPH, benign prostatic hyperplasia; *P. ginseng*, *Panax ginseng*.

untreated group. However, the differences among the groups were not significant (P > 0.05). The total protein levels of the *P. ginseng* group were similar to those of the control group.

Effect of *P. ginseng* on the Prostate

Prostate weight, volume, and weight ratio are shown in Table 3. The prostate weight of the BPH group (1.30 ± 0.05 g) was significantly higher than that of the control group (1.01 ± 0.03 g; P < 0.001), and the *P. ginseng*-treated group (0.97 ± 0.06 g) displayed a significantly lower prostate weight than the BPH group (P < 0.001).

The prostate volume of the BPH group (1.75 ± 0.15 cm³) was significantly higher than that of the control group (0.97 ± 0.11 cm³), and the *P. ginseng*-treated group (0.93 ± 0.14 cm³) dis-

played a significantly lower prostate volume than the BPH group (P < 0.001).

The prostate weight ratio of the BPH group (0.38 ± 0.03 mg/100 g of body weight [BW]) was significantly higher than that of the control group (0.28 ± 0.01 mg/100 g of BW), and the *P. ginseng*-treated group (0.27 ± 0.02 mg/100 g of BW) displayed a significantly lower prostate weight ratio than the BPH group (P < 0.001).

Effect of *P. ginseng* on the Histopathology of the Prostate Tissue

As shown in Fig. 1, the histoarchitecture of the prostate tissue in the BPH group was disrupted. The epithelial cell layer and stromal cell space in the BPH group were larger than those of

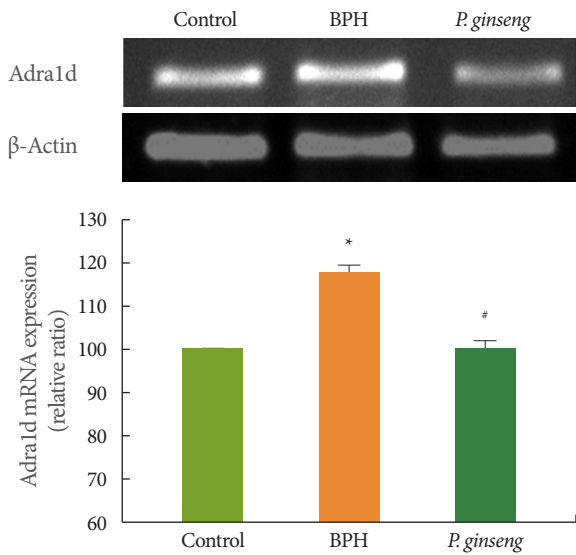


Fig. 2. Alpha-1D adrenergic receptor (Adra1d) mRNA expression of prostate tissue in each group. * $P < 0.05$ compared with control group. # $P < 0.05$ compared with BPH group. BPH, benign prostatic hyperplasia; *P. ginseng*, *Panax ginseng*.

the control group. Compared to the BPH group, the *P. ginseng* group showed reduced stromal cell hyperplasia and epithelial layer thickness.

Effect of *P. ginseng* on Adra1d mRNA Expression in Prostate Tissue

At 4 weeks, the BPH group displayed high Adra1d mRNA expression levels compared to the control group (Fig. 2). At 4 weeks, the *P. ginseng* group displayed significantly lower ($P < 0.05$) Adra1d mRNA expression than the BPH group.

Effect of *P. ginseng* on the Expression of EGFR and BCL2 in Prostate Tissue

As shown in Fig. 3, the BPH group displayed higher EGFR and B-cell CLL/lymphoma 2 (BCL2) expression in prostate tissues than in the control group. EGFR and BCL2 expression in the *P. ginseng* group was lower than that in the BPH group ($P < 0.05$).

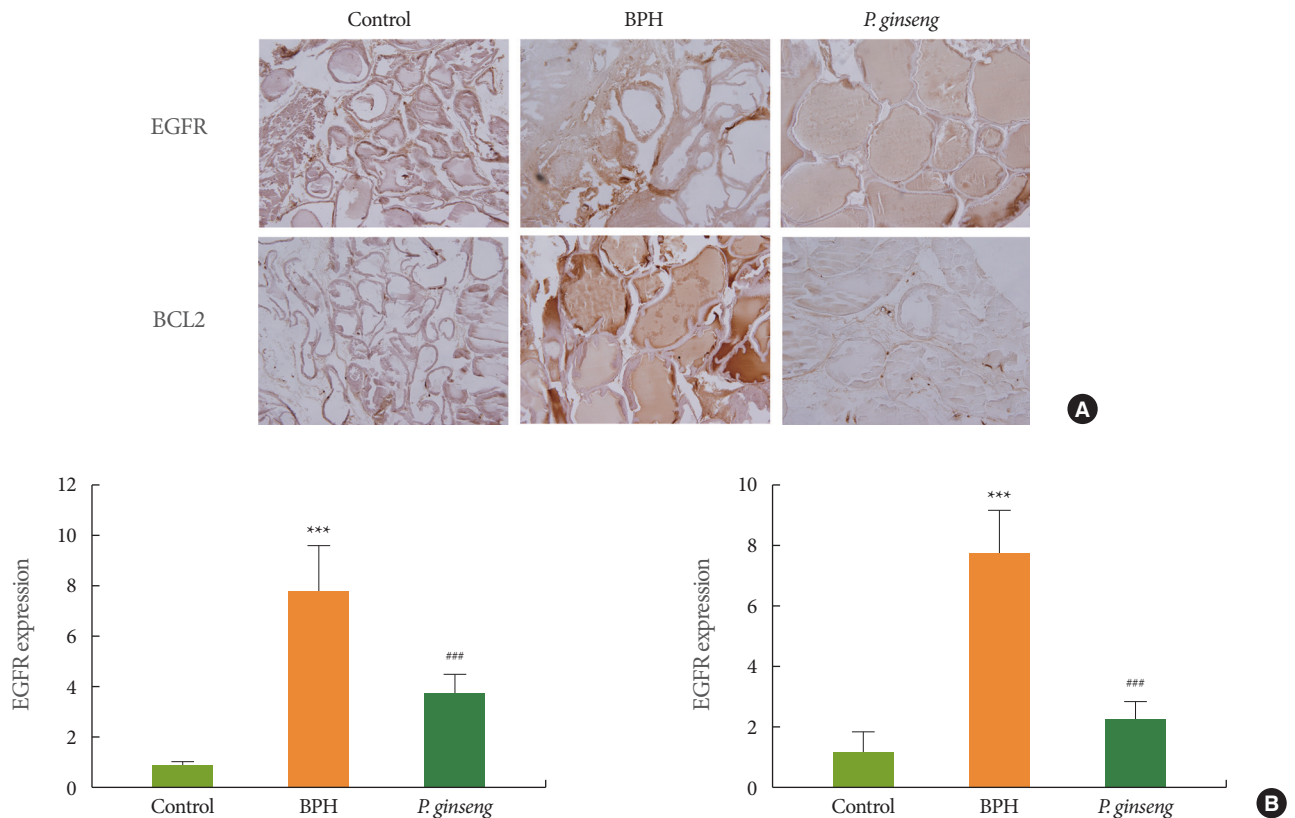


Fig. 3. The expressions of epidermal growth factor receptor (EGFR) and B-cell CLL/lymphoma 2 (BCL2). (A) Immunohistochemistry of prostate tissue from the rats ($\times 10$). (B) The relative ratio of EGFR and BCL2 expression. BPH, benign prostatic hyperplasia; *P. ginseng*, *Panax ginseng*. *** $P < 0.001$ compared with control group. ### $P < 0.001$ compared with BPH group.

DISCUSSION

P. ginseng has been used as a herbal medicine to treat and prevent various diseases for more than 4,000 years. However, to our knowledge, no study has evaluated its inhibitory effect on BPH and the underlying mechanism. In this study, we observed the inhibitory effect of *P. ginseng* on BPH, investigated whether *P. ginseng* influences the alpha-1-adrenergic receptor and the development of BPH in a BPH rat model, and attempted to evaluate the inhibitory effect of *P. ginseng* on prostate hypertrophy.

Alpha-1-adrenergic receptors play important roles in the regulation of prostatic smooth muscle. Thus, they are critical regulators of LUTS and the development of BPH [22,23]. These receptors have been classified into three subtypes, that is, Adra1a, Adra1b, and Adra1d, and have been observed in various tissues, such as the prostate, urethra, bladder, and ureter. These receptor subtypes are differentially localized in human prostate tissue. No difference was observed between the expression of Adra1a and Adra1b in the prostate tissue of control rats and BPH rats [24]. Rats with BPH showed significantly higher Adra1d expression than normal rats. It has been suggested that Adra1d may play a significant role in prostate growth in BPH [24]. There is also evidence that Adra1d is related to mitogen activated kinase-like protein, which mediates cell growth [25]. The mechanism underlying the effect of *P. ginseng* on adrenergic receptors has not yet been studied.

In this study, we observed increased Adra1d expression in the prostate tissue of BPH, and oral administration of *P. ginseng* significantly inhibited increase in Adra1d expression. *P. ginseng* treatment effectively reduced prostate volume compared to that seen for the BPH rats. In addition, we observed that the action of *P. ginseng* is associated with decreased EGFR and BCL2 expression in prostate tissues. EGFR and BCL2 expression was reduced by *P. ginseng*, which is in accordance with the inhibition of BPH development.

Alpha-1-adrenergic receptors also regulate growth and proliferation in various cells. Testosterone or DHT binds to nuclear androgen receptors on the surface of stromal and epithelial cells. It promotes the transcription of growth factors, including epidermal growth factor (EGF) [26,27]. EGFR is the cell surface receptor for members of the EGF family. It regulates diverse biological processes in cell proliferation, differentiation, survival, and apoptosis [28]. Harper et al. [29] reported that increased EGFR have also been associated with the loss of growth control in BPH. Abnormal apoptosis is a known factor in the etiology

of BPH. BCL2 is present in normal basal epithelial cells of the prostate gland and is expressed at significantly higher levels in BPH compared to those in normal prostate tissue. Iacopino et al. [30] also reported that BPH patients overexpress apoptosis-related genes, including BCL2. We found that *P. ginseng* decreased EGFR and BCL2 expression in the prostate tissues of BPH rat models. These observations indicate that *P. ginseng* may effectively inhibit increased EGFR and BCL2 expression and suppress BPH development.

Numerous studies have shown that ginseng contributes to EGFR and BCL2 signaling [31-34]. Sathishkumar et al. [32] used *P. ginseng* to develop inhibitors for the EGFR tyrosine kinase domain. They showed that *P. ginseng* can be used to design new EGFR tyrosine kinase inhibitors. Fu et al. [34] showed that the total saponins in ginseng can protect against hepatic ischemia/reperfusion injury in experimental obstructive jaundice rats.

To summarize, orally administered *P. ginseng* extract was nontoxic and it inhibited the development of prostate hyperplasia and decreased prostate weight in testosterone-induced BPH rat models. We observed that these effects are associated with reduced Adra1d, EGFR, and BCL2 expression. These findings indicate that *P. ginseng* may be inhibiting the alpha1-adrenoceptor to suppress BPH development. Thus, *P. ginseng* may be useful in the treatment of BPH or in the prevention of prostatic hypertrophy. Further studies are required to confirm the involvement of other alpha-1-adrenergic receptors and EGF pathways in BPH.

REFERENCES

1. Lee YJ, Jeong SJ, Byun SS, Lee JJ, Han JW, Kim KW. Prevalence and correlates of nocturia in community-dwelling older men: results from the Korean longitudinal study on health and aging. *Korean J Urol* 2012;53:263-7.
2. Paolone DR. Benign prostatic hyperplasia. *Clin Geriatr Med* 2010; 26:223-39.
3. Lin J, Zhou J, Xu W, Zhong X, Hong Z, Peng J. Qianliening capsule treats benign prostatic hyperplasia via suppression of the EGF/STAT3 signaling pathway. *Exp Ther Med* 2013;5:1293-300.
4. Stroup SP, Palazzi-Churas K, Kopp RP, Parsons JK. Trends in adverse events of benign prostatic hyperplasia (BPH) in the USA, 1998 to 2008. *BJU Int* 2012;109:84-7.
5. O'Leary MP. Lower urinary tract symptoms/benign prostatic hyperplasia: maintaining symptom control and reducing complica-

- tions. *Urology* 2003;62(3 Suppl 1):15-23.
6. Fine SR, Ginsberg P. Alpha-adrenergic receptor antagonists in older patients with benign prostatic hyperplasia: issues and potential complications. *J Am Osteopath Assoc* 2008;108:333-7.
 7. Carson C 3rd, Rittmaster R. The role of dihydrotestosterone in benign prostatic hyperplasia. *Urology* 2003;61(4 Suppl 1):2-7.
 8. Titus MA, Li Y, Kozyreva OG, Maher V, Godoy A, Smith GJ, et al. 5 α -reductase type 3 enzyme in benign and malignant prostate. *Prostate* 2014;74:235-49.
 9. Osman NI, Chapple CR, Cruz F, Desgrandchamps F, Llorente C, Montorsi F. Silodosin: a new subtype selective alpha-1 antagonist for the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia. *Expert Opin Pharmacother* 2012;13:2085-96.
 10. DuBeau CE, Resnick NM. Controversies in the diagnosis and management of benign prostatic hypertrophy. *Adv Intern Med* 1992;37:55-83.
 11. Patel AK, Chapple CR. Medical management of lower urinary tract symptoms in men: current treatment and future approaches. *Nat Clin Pract Urol* 2008;5:211-9.
 12. Akpanabiatu MI, Ekpo ND, Ufot UF, Udoh NM, Akpan EJ, Etuk EU. Acute toxicity, biochemical and haematological study of *Aframomum melegueta* seed oil in male Wistar albino rats. *J Ethnopharmacol* 2013;150:590-4.
 13. Lee MY, Shin IS, Seo CS, Lee NH, Ha HK, Son JK, et al. Effects of *Melandrium firmum* methanolic extract on testosterone-induced benign prostatic hyperplasia in Wistar rats. *Asian J Androl* 2012;14:320-4.
 14. Bae JS, Park HS, Park JW, Li SH, Chun YS. Red ginseng and 20(S)-Rg3 control testosterone-induced prostate hyperplasia by deregulating androgen receptor signaling. *J Nat Med* 2012;66:476-85.
 15. Cho CW, Kim YC, Kang JH, Rhee YK, Choi SY, Kim KT, et al. Characteristic study on the chemical components of Korean curved ginseng products. *J Ginseng Res* 2013;37:349-54.
 16. Cho IH. Effects of Panax ginseng in neurodegenerative diseases. *J Ginseng Res* 2012;36:342-53.
 17. Quan HY, Kim do Y, Chung SH. Korean red ginseng extract alleviates advanced glycation end product-mediated renal injury. *J Ginseng Res* 2013;37:187-93.
 18. Siddiqi MH, Siddiqi MZ, Ahn S, Kang S, Kim YJ, Sathishkumar N, et al. Ginseng saponins and the treatment of osteoporosis: mini literature review. *J Ginseng Res* 2013;37:261-8.
 19. Lim KH, Kang CW, Choi JY, Kim JH. Korean red ginseng induced cardioprotection against myocardial ischemia in guinea pig. *Korean J Physiol Pharmacol* 2013;17:283-9.
 20. Kim YO, Kim HJ, Kim GS, Park HG, Lim SJ, Seong NS, et al. Panax ginseng protects against global ischemia injury in rat hippocampus. *J Med Food* 2009;12:71-6.
 21. Hong SH, Suk KT, Choi SH, Lee JW, Sung HT, Kim CH, et al. Antioxidant and natural killer cell activity of Korean red ginseng (*Panax ginseng*) and urushiol (*Rhus vernicifera* Stokes) on non-alcoholic fatty liver disease of rat. *Food Chem Toxicol* 2013;55:586-91.
 22. Kojima Y, Sasaki S, Hayashi Y, Tsujimoto G, Kohri K. Subtypes of alpha1-adrenoceptors in BPH: future prospects for personalized medicine. *Nat Clin Pract Urol* 2009;6:44-53.
 23. Anglin IE, Glassman DT, Kyprianou N. Induction of prostate apoptosis by alpha1-adrenoceptor antagonists: mechanistic significance of the quinazoline component. *Prostate Cancer Prostatic Dis* 2002;5:88-95.
 24. Kojima Y, Sasaki S, Oda N, Koshimizu TA, Hayashi Y, Kuniwa M, et al. Prostate growth inhibition by subtype-selective alpha(1)-adrenoceptor antagonist naftopidil in benign prostatic hyperplasia. *Prostate* 2009;69:1521-8.
 25. Xin X, Yang N, Eckhart AD, Faber JE. Alpha1D-adrenergic receptors and mitogen-activated protein kinase mediate increased protein synthesis by arterial smooth muscle. *Mol Pharmacol* 1997;51:764-75.
 26. Steiner MS. Review of peptide growth factors in benign prostatic hyperplasia and urological malignancy. *J Urol* 1995;153:1085-96.
 27. Lin J, Zhou J, Xu W, Hong Z, Peng J. Qianliening capsule inhibits benign prostatic hyperplasia angiogenesis via the HIF-1 α signaling pathway. *Exp Ther Med* 2014;8:118-24.
 28. Herbst RS. Review of epidermal growth factor receptor biology. *Int J Radiat Oncol Biol Phys* 2004;59(2 Suppl):21-6.
 29. Harper ME, Glynne-Jones E, Goddard L, Mathews P, Nicholson RI. Expression of androgen receptor and growth factors in premalignant lesions of the prostate. *J Pathol* 1998;186:169-77.
 30. Iacopino F, Angelucci C, Lama G, Zelano G, La Torre G, D'Addessi A, et al. Apoptosis-related gene expression in benign prostatic hyperplasia and prostate carcinoma. *Anticancer Res* 2006;26(3A):1849-54.
 31. Dougherty U, Mustafi R, Wang Y, Musch MW, Wang CZ, Konda VJ, et al. American ginseng suppresses Western diet-promoted tumorigenesis in model of inflammation-associated colon cancer: role of EGFR. *BMC Complement Altern Med* 2011;11:111.
 32. Sathishkumar N, Karpagam V, Sathiyamoorthy S, Woo MJ, Kim YJ, Yang DC. Computer-aided identification of EGFR tyrosine kinase inhibitors using ginsenosides from Panax ginseng. *Comput Biol Med* 2013;43:786-97.
 33. Zhu XY, Zhang ZL, Li P, Liang WY, Feng XR, Liu ML. Shenyan,

an extract of American Ginseng and Corydalis Tuber formula, attenuates cardiomyocyte apoptosis via inhibition of endoplasmic reticulum stress and oxidative stress in a porcine model of acute myocardial infarction. *J Ethnopharmacol* 2013;150:672-81.

34. Fu YQ, Hua C, Zhou J, Cheng BR, Zhang J. Protective effects of ginseng total saponins against hepatic ischemia/reperfusion injury in experimental obstructive jaundice rats. *Pharm Biol* 2013;51:1545-51.