

Butterbur, a herbal remedy, confers complementary anti-inflammatory activity in asthmatic patients receiving inhaled corticosteroids

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Summary

Background The effects of butterbur (BB), a herbal remedy, as add-on therapy to inhaled corticosteroids in patients with atopic asthma is currently unknown.

Objective We evaluated the effects of BB, given as add-on therapy to asthmatic patients maintained on inhaled corticosteroids, assessing adenosine monophosphate (AMP) bronchoprovocation (primary outcome variable) along with other surrogate inflammatory markers such as exhaled nitric oxide, serum eosinophil cationic protein and peripheral blood eosinophil count.

Methods Sixteen atopic asthmatic patients with mean (standard error of mean) forced expiratory volume in 1 s (FEV₁) of 78 (4)% predicted, maintained on their constant dose of inhaled corticosteroids throughout the study, received twice daily for 1 week either BB 25 mg or placebo (PL), in a double-blind, cross-over fashion, with a 1-week washout period prior to each randomized treatment. Measurements were made at baselines prior to each randomized treatment and following the randomized treatment period.

Results Baseline values for the primary and secondary outcomes were not significantly different prior to BB and PL. AMP provocative concentration causing a 20% reduction from baseline FEV₁ (PC₂₀) as doubling dilution change from baseline, significantly improved ($P < 0.05$) with BB, 0.6 (0.2), compared with PL, -0.1 (0.3); a 0.7 doubling dilution difference. Exhaled nitric oxide as change from baseline was significantly reduced ($P < 0.05$) with BB, -1.2 (0.8) p.p.b., compared with PL, 0.5 (0.4) p.p.b. Both serum eosinophil cationic protein and peripheral blood eosinophil count as change from baseline were also significantly suppressed ($P < 0.05$) with BB, -3.9 (3.3) $\mu\text{g/L}$, -31 (28) $\times 10^6/\text{L}$ compared with PL, 3.3 (2.5) $\mu\text{g/L}$, 38 (16) $\times 10^6/\text{L}$, respectively.

Conclusion Chronic dosing with BB conferred complementary anti-inflammatory activity in atopic asthmatic patients maintained on inhaled corticosteroids. Further studies are now required to assess the potential role for BB as either monotherapy in milder patients or add-on therapy in more severe asthmatics.

Keywords adenosine monophosphate, asthma, butterbur, exhaled nitric oxide, herbal remedy, inhaled corticosteroids, peripheral blood eosinophil count, *Petasites hybridus*, petasin, serum eosinophil cationic protein

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Introduction

A herbal remedy known as butterbur (BB) or *Petasites hybridus* has been used to treat many conditions ranging from plague and fever in the middle ages to skin wounds and allergy in the 17th century. BB grows well during warm weather, with its leaves spanning up to a metre in diameter, and its name is attributed to the large leaves being used to wrap butter (Fig. 1). In a recent non-placebo-controlled trial, BB was demonstrated to be as effective as H₁-antihistamine therapy in the treatment of seasonal allergic rhinitis using patient symptom as the outcome measure [1]. Using a

randomized double-blind placebo-controlled cross-over design, we have recently shown that *in vivo*, BB attenuated nasal adenosine monophosphate (AMP) responsiveness in patients with seasonal allergic rhinitis [2]. Both the upper and lower airways are now well recognized as being part of a unified airway [3]. It is also appreciated that diseases and treatments that affect the upper airway will impact on the lower airway and *vice versa* [4]. There have been no randomized placebo-controlled trials to date assessing the effects of BB as add-on therapy in patients with atopic asthma. Bronchoprovocation with AMP is a comprehensively validated challenge correlating well with allergic airway disease and commonly used to assess anti-inflammatory properties of drug therapy [5–8].

We therefore elected to study the effects of BB given as add-on therapy to asthmatic patients already maintained on inhaled corticosteroids, assessing bronchial provocation with AMP as the primary outcome variable along with other

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Fig. 1. Picture of BB (*Petasites hybridus*).

surrogate inflammatory markers such as exhaled nitric oxide, serum eosinophil cationic protein and peripheral blood eosinophil count.

Methods

Patients

Atopic asthmatic patients were required to be stable on inhaled corticosteroids for at least 3 months prior to the study without any change in their usual therapy. The maximum dose of inhaled corticosteroids allowed was 2000 µg of beclomethasone dipropionate/budesonide or 1000 µg of fluticasone propionate. Patients were required to demonstrate sensitization to at least two common aeroallergens including house dust mite on skin prick testing. All had to exhibit airway hyper-responsiveness to inhaled AMP with a provocative concentration causing a 20% reduction from baseline forced expiratory volume in 1 s (FEV₁) (PC₂₀) of less than 200 mg/mL. Patients did not have any symptoms or were being treated for concomitant allergic rhinitis. None of the patients were receiving leukotriene receptor antagonist, theophylline, H₁-antihistamine or intranasal corticosteroids. Informed consent was obtained for all patients and the Tayside Committee on Medical Research Ethics approved the study.

Study design

A randomized, double-blind, placebo-controlled, cross-over design was employed for the study, which was conducted out

of the pollen season, so as to avoid any potential confounding effects in those patients who were sensitized to pollen aeroallergens before. Patients were required to stop their long-acting β_2 -agonists ($n = 6$) during a 1-week washout period prior to the study and for the entire duration of the study. Patients were randomized to receive twice daily (08:00 and 22:00 hours) either BB 25 mg (Petaforce[®], Bioforce Ltd, Irvine, UK) or placebo (PL) for 1 week. Patients took the study medication, which were encapsulated and identical in external physical appearance, at 08:00 hours and attended the department at 10:00 hours the same day. There was a 1-week washout period between the randomized treatments. Patients continued on their usual dose of inhaled corticosteroids throughout the entire study. Measurements were made at baselines after washout prior to each randomized treatment and following each randomized treatment period.

Measurements

Skin prick testing

A standard protocol (Bencard Testing Solutions, Welwyn Garden City, UK) was employed using grass, tree, weed, house dust mite, aspergillus, feather, dog and cat extracts, in addition to a histamine-positive and saline-negative control. A weal diameter of at least 3 mm greater than the negative control was defined as a positive reaction to the particular aeroallergen.

AMP bronchial challenge

This was performed as previously described [9], with AMP being administered to patients via inhalation at 90-s intervals in doubling concentrations from 0.09 to 800 mg/mL until PC₂₀ was achieved.

Spirometry

The American Thoracic Society criteria [10] were employed using a Vitalograph[®] compact spirometer (Vitalograph Ltd, Buckingham, UK) with a computer-assisted pneumotachograph head and pressure transducer. Calibration of the spirometer was carried out daily using a Vitalograph[®] 1 L precision syringe.

Exhaled nitric oxide

Measurements were performed as previously described [11] using an integrated LR2000[®] clinical real-time nitric oxide gas analyser (Logan Research, Rochester, UK) with a flow rate of 250 mL/min and an accuracy of 2 p.p.b. nitric oxide with a response time of 2 s.

Serum eosinophilic cationic protein

Analyses were performed using a radioimmunoassay kit (Pharmacia and Upjohn Diagnostics, Milton Keynes, UK) with an interassay coefficient of variability of 2.7%.

Peripheral blood eosinophil count

Blood samples were examined using a SE9000[®] haematology analyser (Sysmex UK Ltd, Milton Keynes, UK).

Table 1. Baseline mean (standard error of mean) values for the primary and secondary outcome measures

	BB	PL
AMP PC ₂₀ (mg/mL)	51 (12)	65 (19)
FEV ₁ (L)	2.40 (0.15)	2.41 (0.16)
FEF ₂₅₋₇₅ (L/s)	2.10 (0.19)	2.15 (0.22)
PEF (L/min)	410 (20)	411 (20)
Exhaled nitric oxide (p.p.b.)	6.7 (1.1)	6.1 (1.2)
Eosinophil cationic protein (µg/L)	24.5 (3.4)	20.7 (3.5)
Peripheral blood eosinophil count ($\times 10^6/L$)	350 (40)	314 (35)

BB, butterbur; PL, placebo; AMP, adenosine monophosphate; PC₂₀, provocative concentration causing a 20% reduction from baseline FEV₁; FEV₁, forced expiratory volume in 1 s; FEF₂₅₋₇₅, forced expiratory flow at 25–75% of maximal lung volume; PEF, peak expiratory flow.

Statistical analysis

The study was powered at 80% with a sample size of 16 completed patients in a cross-over design. The α -error was set at 0.05 (two-tailed) in order to detect a one doubling dilution difference in AMP PC₂₀ (the primary outcome variable) between randomized treatments. An overall multifactorial analysis of variance was performed followed by multiple-range testing with Bonferroni correction (set at 95% CI). AMP PC₂₀ data were logarithmically transformed to normalize distribution, and analyses were performed using a Statgraphics® statistical software package (STSC Software Publishing Group, Rockville, MD, USA).

Results

Baseline values for the primary and secondary outcome measures were not significantly different comparing BB and PL (Table 1).

Patients

The number of patients that were enrolled and completed the study totalled 16, of which seven were female patients. The mean (standard error of mean) age of the patients was 45 (3) years and all were atopic with sensitization to at least two common aeroallergens, including house dust mite on skin prick testing. All patients were receiving inhaled corticosteroids as part of their asthma therapy. The mean daily doses of inhaled corticosteroids were beclomethasone dipropionate ($n = 11$): 491 (65) µg; budesonide ($n = 2$): 600 (67) µg; and fluticasone propionate ($n = 3$): 542 (103) µg. Patients had a mean FEV₁ at recruitment of 2.51 (0.19) L (78 (4)% predicted) and a geometric mean AMP PC₂₀ of 65 (11) mg/mL.

Bronchial hyper-responsiveness

AMP PC₂₀ as doubling dilution change from baseline was significantly improved ($P < 0.05$) with BB 0.6 (0.2) compared with PL -0.1 (0.3): a 0.7 doubling dilution difference (Fig. 2).

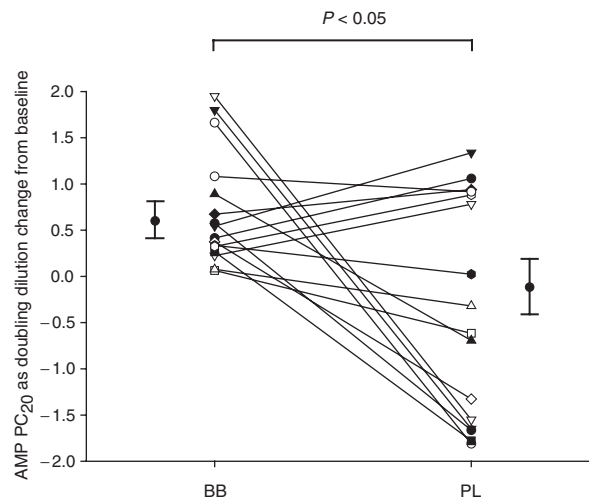


Fig. 2. Individual data for AMP PC₂₀ values as doubling dilution change from baseline, with mean and standard error of mean. Data points for each individual are joined together. BB significantly improved ($P < 0.05$) AMP PC₂₀ compared with PL.

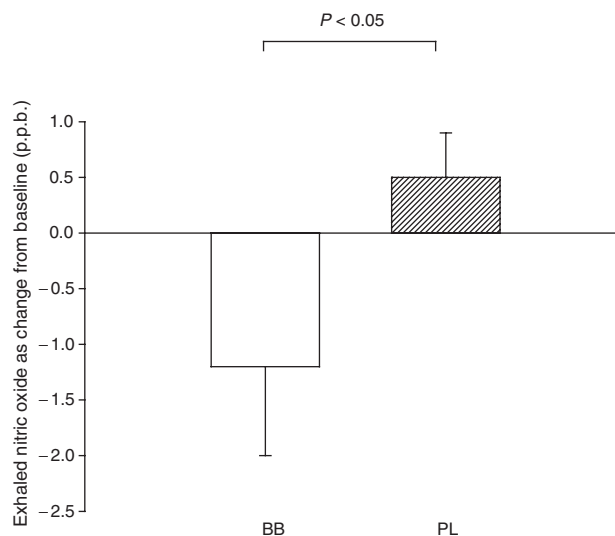


Fig. 3. Mean exhaled nitric oxide as change from baseline (p.p.b.), with standard error of mean. BB significantly suppressed ($P < 0.05$) exhaled nitric oxide compared with PL.

Spirometry

Pre-challenge lung function as change from baseline was not significantly different comparing BB vs. PL; FEV₁, 0.07 (0.04) vs. -0.03 (0.05) L; forced expiratory flow at 25–75% of maximal lung volume (FEF₂₅₋₇₅), 0.04 (0.07) vs. -0.07 (0.08) L/s; peak expiratory flow (PEF), 4 (9) vs. 2 (9) L/min, respectively.

Inflammatory markers

Exhaled nitric oxide as change from baseline was significantly reduced ($P < 0.05$) with BB, -1.2 (0.8) p.p.b., compared with PL, 0.5 (0.4) p.p.b. (Fig. 3). Both serum eosinophil cationic protein and peripheral blood eosinophil count as change from baseline were also significantly suppressed ($P < 0.05$) with BB,

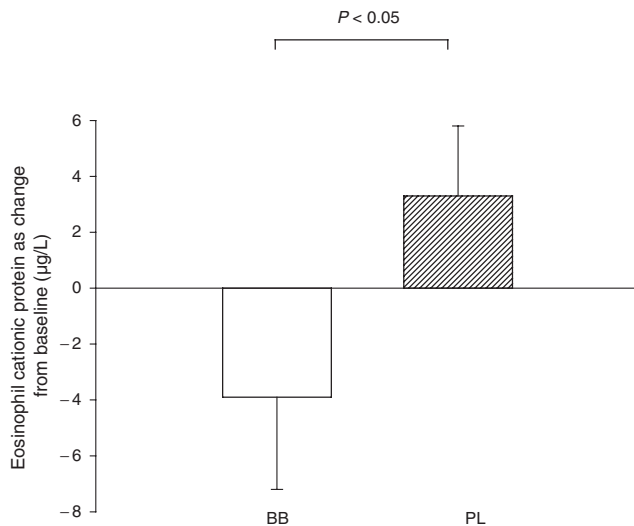


Fig. 4. Mean serum eosinophil cationic protein as change from baseline ($\mu\text{g/L}$), with standard error of mean. BB significantly suppressed ($P < 0.05$) serum eosinophil cationic protein compared with PL.

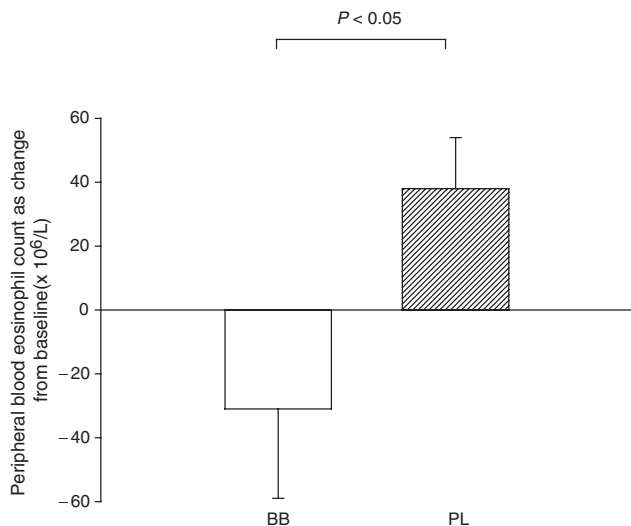


Fig. 5. Mean peripheral blood eosinophil count as change from baseline ($\times 10^6/\text{L}$), with standard error of mean. BB significantly suppressed ($P < 0.05$) peripheral blood eosinophil count compared with PL.

– 3.9 (3.3) $\mu\text{g/L}$, – 31 (28) $\times 10^6/\text{L}$, compared with PL, 3.3 (2.5) $\mu\text{g/L}$, 38 (16) $\times 10^6/\text{L}$, respectively (Figs 4 and 5).

Discussion

Our results show for the first time the effects of BB in patients with atopic asthma maintained on inhaled corticosteroids. BB significantly improved the primary outcome of AMP bronchial hyper-responsiveness and suppressed other surrogate inflammatory markers.

We were careful to conduct our study off the pollen season in order to avoid pollen sensitization being a confounding factor. It is however pertinent to note that none of our patients had any symptom nor were they on any treatment to suggest concomitant allergic rhinitis. It was felt important to employ this in our study as we wanted to assess the effects of

BB purely on the lower airway independent of any effects on the upper airway, although we acknowledge that a possible degree of sub-clinical non-symptomatic nasal inflammation may exist in view of sensitization to perennial aeroallergens such as house dust mite.

Inflammatory mediators such as cysteinyl leukotrienes and histamine in primed mast cells are released following provocation with AMP, resulting in bronchoconstriction. We have shown that BB 25 mg twice daily improved the bronchial AMP PC_{20} , which is in alignment with our previous *in vivo* study where BB 50 mg twice daily attenuated the response to nasal AMP provocation [2]. BB inhibits the biosynthesis of cysteinyl leukotrienes *in vitro* [12–15] and this has translated into *in vivo* attenuation of AMP bronchial hyper-responsiveness, in keeping with previous studies showing improvements in AMP PC_{20} following treatment with montelukast, a leukotriene receptor antagonist [16, 17]. In addition, BB has also been shown to decrease nasal levels of histamine and cysteinyl leukotrienes *in vivo* [18]. The positive effects on bronchial hyper-responsiveness exhibited with BB would have been independent of the influence of airway geometry as pre-challenge FEV_1 values were not significantly different following each randomized treatment period. Moreover, there were no carry-over effects of the randomized treatments as evidenced by the similar baseline values after each washout period for the primary and secondary outcomes (Table 1).

We observed a mean difference of 0.7 doubling dilution in AMP PC_{20} with BB, compared with a mean difference of 1.0 doubling dilution previously observed with montelukast [19, 20], both as add-on therapy to inhaled corticosteroids. It would therefore be interesting to perform a dose–response study with BB as add-on therapy, to see if higher doses would produce a greater change in AMP PC_{20} .

We did not feel it was indicated to assess daily asthma symptoms or rescue medication requirement as our patients were stable and controlled on their current asthma therapy. Moreover, any potential beneficial effects on asthma diary outcomes would not have translated into meaningful clinical observations as our patients were hardly symptomatic to begin with.

BB suppressed exhaled nitric oxide, serum eosinophil cationic protein and peripheral blood eosinophil count compared with PL. The anti-inflammatory activity of BB may be explained by its effects on cysteinyl leukotrienes. Accordingly, we have previously demonstrated significant suppression of both exhaled nitric oxide and peripheral blood eosinophil count with montelukast [19, 21].

In conclusion, chronic dosing with BB conferred complementary anti-inflammatory activity in atopic asthmatic patients maintained on inhaled corticosteroids. Further studies will now be required to assess the potential role for BB as either monotherapy in milder patients or add-on therapy in more severe asthmatics.

Acknowledgements

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