Antitussive Activity of the Ethanolic Extract of *Paederia foetida* (Rubiaceae family) in Non-Anaesthetized Cats

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Abstract

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The aim of the present study was to examine the antitussive activity of the ethanolic extract of *Paederia foetida* (*P. foetida*) in conscious cats by mechanical stimulation of laryngopharyngeal (LP) and tracheobronchial (TB) mucous areas of airways.

The results showed that the ethanolic extract of *P. foetida* at the oral dose of 200 $mg \cdot kg^{-1}$ b.w. had a cough-suppressive effect. It caused a significant ($p < 0.05$) decrease of the number of cough efforts (NE) and frequency of cough ($NE.min^{-1}$) from both LP and TB areas. The intensity of a cough attack was significantly decreased only during inspirium (IA^-). Also a significant ($p < 0.05$) decrease was observed of the intensity of maximal effort in expirium (IME^+) from TB area and inspirium (IME^-) from both LP and TB areas.

The antitussive activity of the ethanolic extract of *P. foetida* was lower than that of the classical narcotic antitussive drug - codeine, but similar to that of the non-narcotic antitussive agent dropropizine. The antitussive activity of the ethanolic extract of *P. foetida* may be connected with its previously demonstrated anti-inflammatory activity.

Cough, antitussive activity, Paederia foetida, codeine, dropropizine, conscious cats

Cough is a protective reflex mechanism removing foreign materials and secretions from the airways (foreign objects, mucus secreted during catarrhs of the respiratory system). However, in various situations it may be inappropriately stimulated, e.g. by inflammation in the respiratory tract, bronchial asthma or by neoplastic processes. In these cases cough is pathological and in some cases it is the reason for using cough-suppressing drugs. Antitussive agents are predominantly used for the suppression of dry and painful cough that disturbs the patient. It is notable that the use of this group of drugs is associated with the suppression of only one symptom, without influencing the underlying condition. Therefore, the administration of this kind of drugs should be prevented in cough associated with bronchiectasis or chronic bronchitis, because of possible harmful thickening of sputum and its retention. In the treatment of these patients agents are preferred with expectorant activity (secretolytics, secretomotorics and mucolytics), that suppress cough by other mechanisms (Rang et al. 1999; Ševecová and Čalkovská 2002).

Widely used antitussives in clinical conditions belong to the group of narcotic analgesics - so-called "codeine group". Their antitussive action is very strong at doses lower than those required for pain relief. Despite of their excellent efficacy they are associated with a relatively high rate of undesirable side effects, such as depression of the respiratory center, decreased mucus secretion in bronchioles, as well as inhibition of ciliary activity. Furthermore, their administration can lead to an increase of sputum viscosity, decrease of

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expectoration, hypotension and constipation. Therefore it is important to explore other non-narcotic substances preventing the pathological cough (Rang et al. 1999) .

Our interest was focused on the antitussive activity of ethanolic extract of *Paederia foetida*, locally known as "Gandhavadulia" (English name "skunkvine"). The decoction of the whole plant is traditionally used in Ayurveda medicine for the treatment of various diseases. *Paederia foetida* Fam. Rubiaceae (Bengali. Gandhavadulia, Eng. Skunkvine) is a perennial woody plant that is typically a climbing vinelike plant in the subtropical and tropical parts of Eastern and Southern Asia as well as in the southern parts of USA (Florida). The plant smells more or less like skunk. Skunkvine flowers are small pink or lilac; leaves are rounded-to-heart-shaped. The fruits are small, shiny brown orbs with two black seeds.

Although various characteristics of *P. foetida* were already reported such as anti-inflammatory and hepatoprotective effects (De et al. 1993), there is no valid information about its antitussive activity. In our previous experiments we tested various plant extracts for their antitussive activity (*Althaea officinalis* L., *Rudbeckia fulgida, Mahonia aquifolium, Arctium lappa, Malva mauritiana* and others), based especially on their polysaccharide structure (Kardošová et al. 1997, 2001, 2002, 2003; Nosáľová et al. 1992, 1993, 1994, 2000; Franova et al. 1998) as well as that of typically found in Bangladesh (*Emblica officinalis*, Nosáľová et al. 2003).

It is widely known that anti-inflammatory properties of various substances participate in their antitussive activity (Korpáš a Nosáľová 1991). Due to the fact that in literature there are no references about the antitussive activity of *P. foetida,* we decided to fill in this information gap and assess whether this plant possesses also other effect(s), that could be potentially used in therapy of pathological forms of the cough.

The aim of this study was to evaluate the antitussive activity of ethanolic extract of *P. foetida* (EEPF) in conscious cats using the method of mechanically induced cough (Korpáš and Nosáľová 1991) and to compare it with other known antitussives.

Materials and Methods

Extraction of plant materials

Five kg of dried whole plant (without roots, collected in spring months from Chittagong, Bangladesh) of *P. foetida* (Voucher sp. No. BC0107) was sopped in absolute ethanol for 15 days and then solvent was filtered off. Then the solvent was evaporated *in vacuo* at 40 °C and the residue was dried at 20 °C under vacuum for 96 hours. The final yield was 16.78%.

Doses and route of administration

The ethanol extract of *P. foetida* was given orally (p.o.) dissolved in water for injection (Biotika, Slovakia), and the dose of EEPF was 200 $mg \cdot kg^{-1}$. This dose was selected according to our previous experiences from antitussive tests with other plant extracts (Nosáľová et al. 1992, 2000, 2003; Kardošová et al. 2002).

Animals

We used nine healthy conscious cats of both sexes 1-3 years old, weighing 1500 - 3000 g, to eliminate the possible effect of an anesthetic on cough reflex. The animals were bought from private breeders and located in faculty animal house for three weeks of quarantine. During the whole experiment, food and water were available *ad libitum.* All experiments were approved by local Ethical Committee at Jessenius Faculty of Medicine Comenius University in Martin and conducted in accordance with basic ethical norms and Helsinki Declaration of 1975, revised in 1983.

Experimental procedure

According to the procedure described in monograph by Korpáš and Nosáľová (1991), the cough was evoked using a nylon fiber 0.35 mm in diameter by five consecutive mechanical irritations of laryngopharyngeal (LP) and tracheobronchial (TB) mucous areas of the airways in experimental animals. The changes of the lateral tracheal pressure were monitored and registered by surgically implanted chronic tracheal cannula. The single cough indicators were reviewed from registered pressure changes (Mingograph Elema device). We evaluated the number of cough efforts (NE), the intensity of the cough attack during expiration (IA^+) and inspiration (IA^-), the cough frequency ($NE.min^{-1}$) and the intensity of maximal cough efforts during expiration (IME^+) and inspiration (IME^-). Control (C) values for each cat were obtained by irritation before the application of the substance. The cough was evoked 0.5, 1, 2 and 5 h after administration of the substance. The quantitative characteristic of the cough suppressive effect was expressed as antitussive activity (in per cent) (Korpáš and Nosáľová 1991).

Statistical analysis

Non-parametric Wilcoxon test was used for the statistical analysis of the results. The results are presented as mean ± standard error of the mean (SEM). Significance of $p < 0.05$ and $p < 0.01$ is shown by one and two asterisks, respectively.

Results

By mechanical provocation of cough a significant reduction of the number of cough efforts (NE) in laryngopharyngeal (LP) area 30 min ($p < 0.05$), and 1, 2 and 5 h ($p < 0.01$) after the administration of an oral dose of 200 mg·kg^{-1} body weight (b.w.). Similarly, the significant reduction of NE in tracheobronchial (TB) area of the airways 30 min, 1 h ($p < 0.01$), and 2 h ($p < 0.05$) after administration of this substance was observed. The reduction of NE from TB area 5 hours after administration was not significant (Fig. 1).

EEPF at the oral dose of 200 mg·kg^{-1} b.w. significantly decreased the cough frequency from both irritated areas of the airways (Fig. 2).

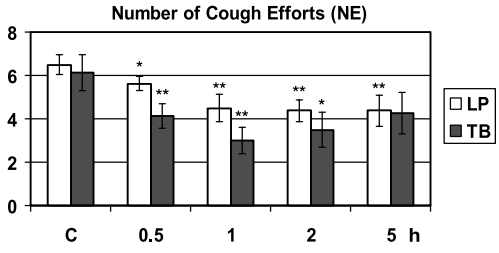

Fig. 1. Number of cough efforts (NE) recorded in Control (C marks values before application of tested substance) and 0.5, 1, 2 and 5 hours after administration of 200 mg·kg^{-1} b.w. of ethanolic extract of *P. foetida* p.o. LP columns represent mean values of cough parameter from laryngopharyngeal area stimulation; TB columns represent mean values of cough parameter of tracheobronchial area stimulation. The range means the standard error of the mean (± S.E.M.). Asterisks represent statistical significance according to paired Student's *t*-test (*$p < 0.05$, **$p < 0.01$).

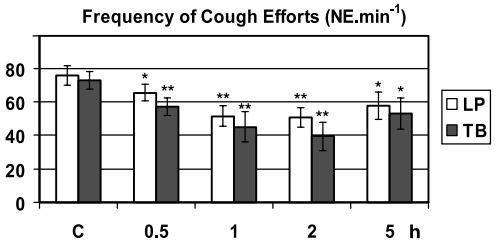

Fig. 2. Frequency of cough efforts (NE.min^{-1}) after the administration of 200 mg·kg^{-1} b.w. of EEPF p.o. For explanation see Fig. 1.

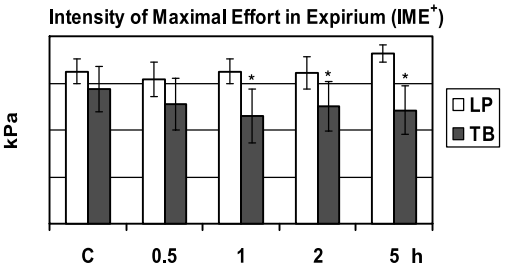

Fig. 3. Intensity of maximal cough effort in exspirium (IME$^+$) after the administration of 200 mg·kg^{-1} b.w. of EEPF p.o. For explanation see Fig. 1.

The registered effects of EEPF on the intensity of maximal effort in expiration (IME$^+$, see Fig. 3) showed a significant decrease only in TB area. There was no reduction of IME$^+$ in LP area. The intensity of maximal effort in inspiration (IME$^-$) showed a significant decrease in both irritated areas 30 min, 1 and 5 h ($p < 0.01$), as well as 2 h ($p < 0.05$) after administration of 200 mg·kg^{-1} b.w. of EEPF (Fig. 4).

There was no significant change observed in the intensity of cough attack during

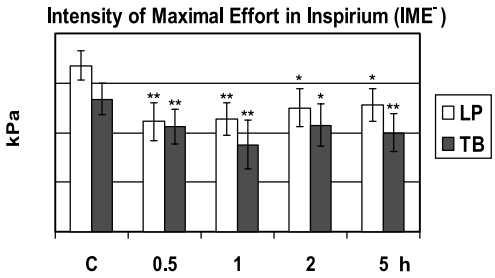

Fig. 4. Intensity of maximal cough effort in inspirium (IME^-) after the administration of 200 mg·kg^{-1} b.w. of EEPF p.o. For explanation see Fig. 1.

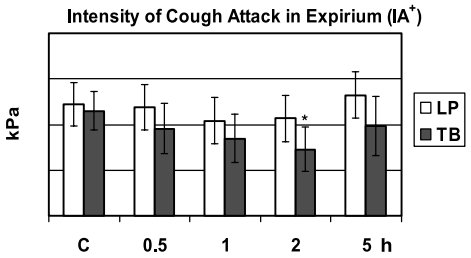

Fig. 5. Intensity of cough attack during expirium (IA^+) after the administration of 200 mg·kg^{-1} b.w. of EEPF p.o. For explanation see Fig. 1.

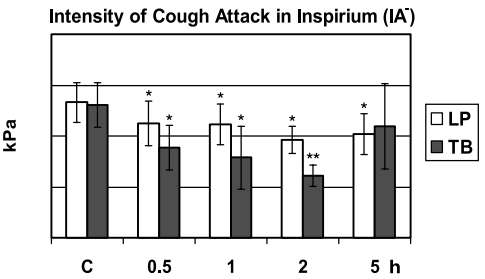

Fig. 6. Intensity of cough attack during inspirium (IA^-) after the administration of 200 mg·kg^{-1} b.w. of EEPF orally. For explanation see Fig. 1.

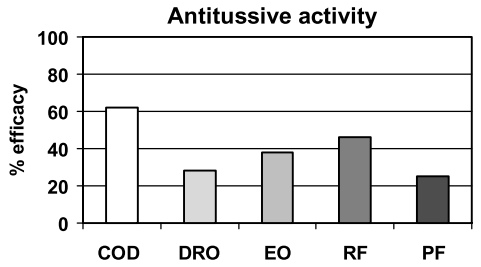

Fig. 7. Comparison of antitussive activity of codeine in the dose of 10 mg·kg^{-1} b.w. (COD), dropropizine at the dose of 100 mg·kg^{-1} b.w. (DRO), *E. officinalis* at the dose of 200 mg·kg^{-1} b.w. (EO), *Rudbeckia fulgida* at the dose of 50 mg·kg^{-1} b.w. (RF), and ethanolic extract of *P. foetida* at the dose of 200 mg·kg^{-1} b.w. (PF) in conscious cats.

expiration (IA^+) in LP area. The stimulation of TB area caused a decrease of IA^+, but this was significant only 2 hours after administration of the substance (Fig. 5). The intensity of cough attack in inspiration (IA^-) was significantly decreased in both irritated areas: in LP area 30 min, 1, 2 and 5 h ($p < 0.05$), and in TB area (Fig. 6) 30 min, 1 h ($p < 0.05$) and 2 h ($p < 0{,}01$) after administration of EEPF.

The antitussive activity of EEPF in the orally administered dose of 200 mg·kg^{-1} b.w. was 25.3%.

Discussion

Extracts of leaves and fruits of *P. foetida* have been used locally in Asia for anti-inflammatory properties in the treatment of arthritis and for its antidiarrheal properties in the therapy of diarrhea or dysentery (Haider et al. 1991). Currently other effects of this plant are known, such as hepatoprotective effect (De et al. 1993), anti-tumour-promoting effect of paederosid present in *P. foetida* leaves (Kapadia et al. 1996), anthelmintic effect (Roychoudhury et al. 1970). Its anti-inflammatory activity was confirmed in several studies (De et al. 1993, 1994; Srivastava et al. 1973) .

Haider et al. (1991) carried out a randomized, double blind, placebo-controlled clinical study to compare the efficacy of *P. foetida* in the therapy of shigellosis with that of ampicillin and placebo. Treatment with this indigenous plant did not show any clinical improvement or bacteriological cure as compared to ampicillin (Haider et al. 1991).

We suppose that some of the pharmacological properties of *P. foetida* mentioned above (especially the anti-inflammatory action) could take part in antitussive efficacy of the ethanolic extract of the *P. foetida*. We observed neither hypersecretion of mucus nor hypersalivation in all experimental cats during our experiments. After the administration of EEPF there was a temporary loss of appetite observed in all cats involved in experiments lasting for one to two days without significant weight loss. The p.o. administration of the dissolved EEPF was connected with aversion, probably due to bad taste or malodour.

In numerous studies for testing of antitussive activity of various plant extracts mice and rats were used (Mandal et al. 2000; Murugesan et al. 2000; Saha et al. 1997; Mukherjee et al. 1997) and cough reflex was provoked by sulfur dioxide or capsaicin (Pecova et al. 2003). In our experiments we chose mechanical stimulation of laryngopharyngeal (LP) and tracheobronchial (TB) mucous areas of airways in cats. We preferred mechanical stimulation to chemical or electrical stimulation because this impulse simulates the natural conditions of cough, induced by foreign solids or saliva. Moreover, it represents point stimulation; the intensity of irritation is constant and the possibility of receptor adaptation to this kind of irritation is unlikely (Nosáľová et al. 1989). The mechanical stimulation of the airways represents objective methods for not only quantitative but also for qualitative evaluation of the antitussive activity. This fact is supported thereby the cats were not anaesthetized in order to eliminate the possible side effects of anesthetics to cough. According to Korpáš and Nosáľová (1991), the cats are the most suitable animals for the cough modeling and the testing of various substances for their effects on the cough reflex.

We observed that EEPF in dose of 200 $mg \cdot kg^{-1}$ b.w. had quite a good potency to inhibit mechanically provoked cough. These effects were observed both in decreasing the number of efforts and intensity of attack, considered to be the most important factors in the predicting of the antitussive activity of any substance. The intensity of maximal effort was influenced significantly, too. This finding could represent a disadvantage from the point of view of expectoration, although this was not observed after administration of EEPF.

A comparison of the cough indicators from TB and LP regions revealed different abilities to influence the mechanisms regulating the quality and quantity of coughing. In all assessed parameters, the decrease observed after administration of EEPF was more significant in TB area.

The result also confirmed our earlier findings that compounds with dominant peripheral mechanisms reduce the frequency of coughing and have much less influence on its amplitude during expiration. The frequency of coughing depends probably on the condition of the cough receptors, whereas the amplitude is determined by the condition of the cough center (Korpáš and Nosáľová 1991; Fraňová et al. 1995, 2000, 2001).

Comparison of the EEPF ability to suppress the cough to commonly used drugs in clinical

practice as well as to other plant extracts is shown in Fig. 7. The excellent cough suppressing activity of centrally acting narcotic antitussive codeine (62%) at a dose of 10 mg·kg^{-1} b.w. intraperitoneally (Strapková et al. 1984) is well known, but is accompanied by various side effects, which could limit its use (Rang et al. 1999). Codeine is used as a reference drug for antitussive activity tests. EEPF at the dose of 200 mg·kg^{-1} b.w. orally had similar antitussive activity as that of dropropizine (28.3%) at the dose of 100 mgxkg^{-1} b.w. intraperitoneally (Nosáľová et al. 1985), widely used non-narcotic antitussive agent in clinical practice. The antitussive activity was lower than that of *E. officinalis* (38.1%) at the same dose of 200 mg·kg^{-1} b.w. orally (Nosáľová et al. 2003) as well as that of orally administered polysaccharide complex isolated from leaves of *Rudbecka fulgida* (46%) at the dose of 50 mg·kg^{-1} b.w. (Nosáľová et al. 2000).

In conclusion, our findings indicate that the antitussive activity of ethanolic extract of *Paederia foetida* in conscious cats is similar to that of commonly used non-narcotic antitussive dropropizine, suggesting its possible therapeutic use. However, further studies need to be done to evaluate its efficacy in clinical conditions.

Antitusická aktivita etanolového extraktu *Paederia foetida* (fam. Rubiaceae) u neanestézovaných mačiek

Cieľom bolo stanoviť antitusickú aktivitu etanolového výťažku Paederia foetida (*P. foetida*) u neanestézovaných mačiek použitím mechanicky indukovaného kašľa z laryngofaryngeálnej (LP) a tracheobronchiálnej (TB) oblasti sliznice dýchacích ciest.

Etanolový extrakt z *P. foetida* v perorálnej dávke 200 mg·kg^{-1} telesnej hmotnosti spôsobil potlačenie mechanického kašľa. Prejavilo sa to významným poklesom počtu nárazov kašľa (NE) a frekvencie kašľa (NE·min^{-1}) z LP ako aj TB slizničnej oblasti dýchacích ciest. Intenzita kašľového ataku bola významne nižšia iba počas inspíria (IA^{-}). Pozorovali sme aj signifikantný pokles sily maximálneho kašľového nárazu v exspíriu (IME^{+}) z TB oblasti a v inspíriu (IME^{-}) z LP ako aj TB oblasti dýchacích ciest.

Autori zistili významnú antitusickú aktivitu etanolového extraktu *P. foetida*, ktorá bola nižšia ako antitusické pôsobenie klasického narkotického antitusika - kodeínu, ale porovnateľná s účinkom nenakrotického antitusika dropropizínu.

Autori predpokladajú, že antitusická aktivita etanolového extraktu *P. foetida* je spojená s jej dokázaným protizápalovým pôsobením. Na potvrdenie tohto predpokladu sú však potrebné ďalšie sledovania.

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