Antitussive activity of the fruit extract of *Emblica officinalis* Gaertn. (Euphorbiaceae)

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Summary

The antitussive activity of *Emblica officinalis* Gaertn. (*E. officinalis*, Fam. Euphorbiaceae) was tested in conscious cats by mechanical stimulation of the laryngopharyngeal and tracheobronchial mucous areas of airways. The results showed that at a dose of 50 mg/kg body wt. perorally, the cough suppressive effect of *E. officinalis* is not unambiguous. A higher dose (200 mg/kg body wt.) of this substance perorally was more effective, especially in decreasing the number of cough efforts (NE), frequency of cough (NE/min⁻¹) and the intensity of cough attacks in inspirium (IA⁺) and expirium (IA⁻) was more pronounced. These results showed that the cough suppressive activity of *E. officinalis* is dose-dependent. We could also demonstrate that the antitussive activity of *E. officinalis* is less effective than shown by the classical narcotic antitussive drug codeine, but more effective than the non-narcotic antitussive agent dropropizine. It is supposed that the antitussive activity of the dry extract of *Emblica officinalis* is due not only to antiphlogistic, antispasmodic and antioxidant efficacy effects, but also to its effect on mucus secretion in the airways.

Key words: cough, antitussive activity, *Emblica officinalis*, codeine, dropropizine, conscious cats

Introduction

The cough is a protective reflex mechanism that removes foreign material and secretions from the bronchi and bronchioles of the airways (foreign objects, catarrh of the respiratory system, etc.). It can be in various situations inappropriately stimulated; for example, by inflammation in the respiratory tract or neoplasia. In these cases, the cough has a pathological character and it is necessary sometimes to use cough-suppressant drugs. The antitussive agents are used mainly to suppress dry, painful and patient-disturbing coughs. It should be mentioned that the use of this group of drugs suppresses only one symptom without influencing the underlying condition. Therefore, we should prevent administration of such a drugs in cough associated with bronchiectasis or chronic bronchitis, because of possible harmful sputum thickening and retention. In these cases, agents with expectorant activity are preferable (secretolytics, secretomotorics and mucolytics), and can suppress cough by other mechanisms (Rang et al. 1999)

The most frequently used antitussive drugs in clinical conditions are from a group of narcotic analgesics. Their antitussive action is very effective at doses below those required for pain relief. Their greatest disadvantage is a high rate of unwanted effects, like depression of the respiratory center, decreased secretion in the bronchioles, and inhibition of ciliary activity. Their administration can lead to increased sputum viscosity, decreased expectoration, hypotension and constipation. All of these side-effects led us to look for other sub-
stances, especially non-narcotic ones, which might prevent the pathological cough (Rang et al. 1999).

Our interest was focused on the antitussive activity of natural substances from fresh fruits of *Emblica officinalis* Gaertn., syn. *Phyllanthus emblica* L. (English names: Indian Goosberry, Emblic Myrobalan; Sanskrit names: Amalaki, Dhatriphala; Hindi names: Amla, Aovla), used traditionally in Ayurvedic medicine. Although various effects of *Emblica officinalis* have already been reported, such as antioxidant and anti-inflammatory effects (Bhattacharya et al. 1999, Asmawi et al. 1993), no report provided reliable information about its antitussive activity.

Many authors have commented on the presence of antitussive activity in various plant extracts, based especially on polysaccharide structure, mainly glucans (Kardošová et al. 2001, Nosál’ová et al. 2000, Nosál’ová et al. 1992, Nosál’ová et al. 1993) or other components (Mandal et al. 2000, Saha et al. 1997). This work presents the results of an antitussive activity test with *Emblica* *officinalis* (*E. officinalis*) and its dose-dependency.

### Material and Methods

#### Extraction of plant materials

Fresh fruits of *Emblica officinalis* Gaertn. (15 kg) were collected from the local market of Chittagong, Bangladesh, in September 1999. They were processed as follows: dried, crushed and the powdered fruits then soaked in absolute ethanol (99.96%) for 15 days. After 15 days the extract was collected, filtered and dried *in vacuo* at 40 °C (yield 15.00%) and then the dried residue was further dried in a vacuum drier at 20 °C for 72 h. The vacuum dried extract was then kept in a freezer in an open container for 7 days. The resultant extract (yield 20.75%) showed a very good water-solvability.

#### Doses and route of administration

The extract of *Emblica officinalis* was given perorally dissolved in water for injection, so the dose of *E. officinalis* was 50 mg/kg body wt. and 200 mg/kg body wt., respectively. These doses were selected according to our previous experiences from antitussive tests with other plant extracts (Nosál’ová et al. 2000, Nosál’ová et al. 1992, Kardošová et al. 2002). For comparison we used the results of cough suppression tests of codeine in doses of 10 mg/kg body wt. intraperitoneally and dropropizine in doses of 100 mg/kg body wt. intraperitoneally, as obtained in our previous experiments (Strapková et al., 1984, Nosál’ová et al. 2000, Nosál’ová et al. 1985, Korpáš and Nosál’ová, 1991).

#### Animals

We used conscious cats of both sexes, weighing 1500–3000 g each, to eliminate the possible effect of anesthetic on cough reflex. There were 8 in each group. All experiments were conducted in accordance with basic ethical norms and the Helsinki declaration from 1975, revised in 1983.

#### The experimental procedure

According to the procedure described in a monograph written by Korpáš and Nosál’ová in 1991, the cough was evoked using a nylon fiber 0.35-mm diameter for five consecutive mechanical irritations of the laryngopharyngeal (LP) and tracheobronchial (TB) mucous areas of the airways in experimental animals. The changes in lateral tracheal pressure were monitored and registered by the surgically implanted chronic tracheal canulla. The single cough parameters were reviewed from registered pressure changes (Mingograph Elema device). We evaluated the number of cough efforts (NE), the intensity of cough attacks 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⁻). The irritation was made before the application of substance, to record the control (C) for each animal. The cough was evoked 0.5, 1, 2 and 5 h after application of substance (Korpáš and Nosál’ová, 1991).

#### Statistical analysis

In order to statistically evaluate the results obtained during the experiments, Wilcoxon’s and Wilcox’s rank test was used (Wilcoxon and Wilcox, 1964). The given columns represent average values; the range means the standard error of the mean (± S.E.M.). Significance of 5% and 1% is shown by dots.

#### Results

Figure 1 shows statistically significant reduction of the number of cough efforts (NE) in the laryngopharyngeal area (LP) 30 min after administration and in the tracheobronchial area (TB) of the airway 30 min and 1 h after administration of *E. officinalis* at a dose of 50 mg/kg body wt., perorally. *E. officinalis* at a dose of 50 mg/kg perorally decreased the cough frequency from both irritated areas of the airways. Statistically more significant was the drop in this parameter for the laryngo-pharyngeal area (Fig. 2). There were registered effects of *E. officinalis* on the intensity of cough attack during expiration (IA⁺, Fig. 3) and inspiration (IA⁻), but a significant change in the intensity of cough attack was observed only 1 h after administration of 50 mg/kg body wt. of *E. officinalis* during inspiration,
for both irritated areas (Fig. 4). There was no significant change in the intensity of maximal cough effort during expiration (IME') and inspiration (IME').

The administration of 200 mg/kg body wt. of *E. officinalis* was accompanied by a significant decrease of NE in the LP area after 0.5, 1, 2 and 5 h and in the TB area after 0.5 and 5 h (Fig. 5). The frequency of cough (NE/min⁻¹) was influenced significantly in both irritated areas (Fig. 6). At the higher dose, the effect of *E. officinalis* on the intensity of the cough attack was also more clear: during expiration (IA⁻) the values in all measured intervals were significantly lower than for control (C) in the TB area (Fig. 7). During inspiration (IA⁻), we observed a significant drop [0.5 and 5 h in the TB area and 1 h in the LP area; Fig. 8]. The intensity of maximal cough effort was almost unreflected.
The comparison of the antitussive effect of *E. officinalis* in both perorally administrated doses (50 mg/kg body wt. = 27.3% vs. 200 mg/kg body wt. = 38.1%) with opioid antitussive codeine at a dose of 10 mg/kg body wt. intraperitoneally (~62%) (Strápeková et al. 1984, Nosál'ová et al. 2000) and the non-narcotic antitussive dropropizine at a dose of 100 mg/kg body wt. intraperitoneally (~28.3%) (Nosál'ová et al. 1985) is shown in Fig. 9.

**Discussion**

Unwanted and often life-complicating side-effects from narcotic antitussive drugs (called also codein's group), such as the attenuation of respiratory center activity, decrease of secretion and increase of sputum viscosity and elasticity, decrease of expectoration, dependence (mainly in children), and bronchoconstriction, among others, are very well-known. The aims of cur-

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**Fig. 5.** Number of cough efforts (NE) after administration of 200 mg/kg body wt. of *E. officinalis*, perorally (For explanation see Fig. 1). ■ LP; □ TB

**Fig. 6.** Frequency of cough efforts (NE/min⁻¹) after administration of 200 mg/kg body wt. of *E. officinalis*, perorally (For explanation see Fig. 1). ■ LP; □ TB

**Fig. 7.** Intensity of cough effort during expiration (IA⁺) after administration of 200 mg/kg body wt. of *E. officinalis*, perorally (For explanation see Fig. 1.). ■ LP; □ TB

**Fig. 8.** Intensity of cough attack during inspirium (IA⁻) after administration of 200 mg/kg body wt. of *E. officinalis*, perorally (For explanation see Fig. 1.). ■ LP; □ TB
rent research are to find new substances or mechanisms, which could influence cough reflex without these side-effects, or to decrease their occurrence as much as possible. The existence of such agents has confirmed the results of our previous research (Nosál'ová et al. 1985, Nosál'ová et al. 1984), particularly in terms of synthetic agents representing the group of non-narcotic cough suppressants. Because we find similar potency in plants (Kardošová et al. 2001, Nosál'ová et al. 2000, Nosál'ová et al. 1992, Nosál'ová et al. 1993), these agents are the subjects of our interest. We chose to follow antitussive activity of Emblica officinalis.

Emblica officinalis Gaertn. (Amla, Aovla, Amalaki, Dhatriphata, Phyllanthus emblica, Indian gooseberry, Emblíc myrobalan) is a tree growing in subtropical and tropical parts of China, India, Indonesia and the Malay Peninsula. Extracts of leaves and fruits of E. officinalis are used in Indian traditional system of medicine, Ayurveda, for antiinflammatory and antipyretic properties or in the treatment of pancreatic disorders or their spasmodic activities (Asmawi et al. 1993, Thorat et al. 1995, Ihantola-Vormisto et al. 1997). Other effects of this plant, like action against free radicals damage induced during stress (Rege et al. 1999), protective effect against chemical carcinogenesis (Jeena et al. 1999, Nandi et al. 1997), protection against genotoxicity induced by aluminium (Al), lead (Pb), and nickel chloride (Dhir et al. 1993, Dhir et al. 1991) better than ascorbic acid, have all been reported. Among other effects are inhibition of lipid peroxidation (Kumar and Muller, 1999), antibacterial effect (Ahmad et al. 1998), antiatherosclerotic and hypolipidemic activity (Mathur et al. 1996, Jacob et al. 1988, Thakur et al. 1988, Thakur, 1985). The water fraction of the methanol extract inhibited migration of human polymorphonuclears and platelets in relatively low concentrations. The data suggest that the plant leaves contain as yet uniden-

Fig. 9. Comparison of antitussive effectiveness of E. officinalis in a dose of 50 mg/kg body wt. (EO50), 200 mg/kg body wt. (EO200), codeine 10 mg/kg body wt. (COD) and dropipazine 100 mg/kg body wt. (DROP) in conscious cats.
dioxide, in our experiments we chose the mechanical stimulation of laryngopharyngeal and tracheobronchial mucous areas of airways in cats. We preferred mechanical stimulation to chemical or electrical stimulation because this method simulates the natural conditions of cough, induced by foreign solids or saliva. Moreover, it is point stimulation; the intensity of irritation is constant and the possibility of receptor adaptation to this kind of irritation is unlikely (Nosálová et al. 1989). The chemical and electrical impulses of the airway do not have these facilities. The mechanical stimulation of the airways represents an objective method for not only quantitative but also qualitative evaluation of the antitussive activity. Therefore, the cats were not anaesthetized in order to eliminate any possible side-effects of anesthetics on cough. According to Korpáš and Nosálová (1991), cats are the most suitable animals for cough modeling and testing of various substances for their effect on the cough reflex.

E. officinalis seems to have a quite good ability to inhibit mechanically-provoked cough, but only at higher doses (200 mg/kg body wt.). These effects were observed especially in the decreasing number of efforts and intensity of attacks during expiration, which are considered to be the most important predictors of antitussive activity of any substance. The intensity of maximal effort was not influenced significantly. This finding is advantageous from the point of view of expectoration. Furthermore, this fact could be explained by a peripheral mechanism of cough suppression.

A comparison of cough parameters from TB and LP regions revealed different abilities to influence the mechanisms regulating the quality and quantity of cough. The result also confirmed our earlier findings that compounds with dominant peripheral mechanisms reduce the frequency of cough and have much less influence on its amplitude. The frequency of cough depends probably on the condition of the cough receptors, while the amplitude is determined by the condition of the cough center (Korpáš and Nosálová, 1991, Fraňová et al. 1995, Fraňová, 2000).

The ability of E. officinalis in various doses to suppress cough parameters was compared to commonly used drugs in clinical practice. The excellent cough-suppressing activity of codeine, a centrally-acting narcotic antitussive drug, is well-known but accompanied by various side-effects which could limit its use (Rang et al. 1999). Another known antitussive, dropropizine, a non-narcotic antitussive, has in an i.p. dose of 100 mg/kg body wt. significantly lower activity than codeine, but fewer unwanted effects. The tested substance, E. officinalis in a dose of 50 mg/kg body wt., had antitussive activity similar to dropropizine. This dose was selected for better comparison with the antitussive activity of other plant extracts, as most of them are tested at this dosage. An experimental increase of dose up to 200 mg/kg body wt. was connected with enhanced antitussive activity, which was still lower than that of codeine but more effective than that of dropropizine.

In conclusion, we can report the presence of antitussive activity of E. officinalis in conscious cats, which is dose-dependent but higher than the antitussive activity of the commonly used non-narcotic antitussive dropropizine.

Acknowledgements
This work was supported by VEGA grant No. 1/8155/01. The author M.T.H.K. would like to acknowledge the “South-South Fellowship” program of the Third World Academy of Sciences (TWAS), Italy, for his travel support to visit Pakistan.

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