

Review

Herbal polysaccharides and cough reflex[☆]Gabriela Nosalova^a, Dana Fleskova^a, Ludovit Jurecek^a, Vladimira Sadlonova^{a,*}, Bimalendu Ray^b^a Department of Pharmacology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia^b Natural Products Laboratory, Department of Chemistry, The University of Burdwan, India

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ABSTRACT

In the last decades plant substances have become a leading form of treatment of many respiratory symptoms, including cough. It has been shown that compounds purified from polysaccharides from *Adhatoda vasica*, *Withania somnifera*, and *Glycyrrhiza glabra* have various biological activities, such as antioxidant, anti-inflammatory, immunomodulating, antispasmodic action, or antiallergic properties, and they often act as cough suppressants. This work demonstrates new natural substitutes for synthetic antitussives whose application is associated with numerous adverse effects. We investigated pharmacodynamic characteristics of arabinogalactan samples extracted from *A. vasica*, *W. somnifera*, and *G. glabra*. These extracts showed the ability to reduce citric acid-induced cough in awake guinea pigs after oral administration in a dose of 50 mg/kg. The strongest antitussive effect (81%) was found after application of the extract from *G. glabra*. There was a 67% cough suppression with *A. vasica* and 61% with *W. somnifera*, which was comparable with the antitussive activity of codeine (62%).

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1. Introduction

It is generally accepted that medicinal herbs are widely used to alleviate respiratory symptoms. In comparison with previous periods, the recent rational phytotherapy prefers plant remedies with exactly defined chemical composition and structure. According to our previous findings, some natural compounds belonging to alkaloids, flavonoids, saponins, tannins, and terpenoids have anti-tussive and expectorant effects (Nosál'ová et al., 2006). During the last decades, numerous carbohydrate polymers have been shown to be responsible for biological effects via complex reaction cascades (Wang and Quinn, 2010). The natural hydrocolloid composed of complex carbohydrate macromolecules has a wide scale of physicochemical properties which are essential in the traditional medicine and pharmacy. Polysaccharides can have a number of effects including anti-inflammatory, immunostimulating, complement activation, antithrombotic, antidiabetic, and infection protective activities (Thakur et al., 2009). We found that many herbal polysaccharides also exhibit antitussive activity (Nosál'ová et al., 1993, 1994, 2005). Cough belongs to the most important defense reflexes of the organism (Irwin and Madison,

2000). The pharmacological influence on the cough reflex remains still an unresolved problem. Therefore, in the present article we set out to investigate the cough suppressive activities of the arabinogalactans of the plant *Adhatoda vasica*, *Withania somnifera* and *Glycyrrhiza glabra* and to compare them with the archetype synthetic antitussive drug codeine.

2. Materials and methods

2.1. Plant material and preliminary treatments

Leaves of *A. vasica* were collected from the garden of medicinal plants at the University of Burdwan, West Bengal, India. The leaves (10 g) were washed thoroughly with tap water, and then blended with water (800 ml) in a mixer (Waring Products Inc., Torrington, CT, USA). Dried water plant extract contained 89 mol percent of neutral sugars (29 mol percent arabinose and 60 mol percent galactose) and proteins (21 weight percent of fraction dry weight). *A. vasica* also known as Basak is a shrub from the *Acanthaceae* family. This small evergreen shrub has been used in traditional Indian medicine for more than 2000 years, with no serious side effects ever documented (Kapoor, 1990). Juice from the leaves and alcoholic liquid extracts or syrups are used as a remedy for asthma, bronchitis, and chronic cough (Dhuley, 1999; Amin and Mehta, 1959). *A. vasica* also has anti-inflammatory (Chakraborty and Brantner, 2001) and antioxidative properties (Singh et al., 2008; Thakur et al., 2012). The plant contains alkaloids such as vasicine, vasicinone, deoxyvasicine, vasicol, adhatodinine, vasicinol, and others (Prasad, 2010). The alkaloid vasicine showed bronchodilatory activity in both *in vitro*

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and *in vivo* assays. Nemčková et al. (1998) showed that ambroxol, a semisynthetic derivative of vasicine from *A. vasica*, has cough suppressive activity in experimental conditions. Structural features of arabinogalactans have already been detected (Chattopadhyay et al., 2011). The present study was focused on the antitussive activity of water extracted polysaccharides isolated from the *A. vasica* leaves.

G. glabra L., locally known as Jasthimadhu, liquorice, or sweet wood has a long history. The roots of this shrub are the main source of drug preparation. In modern medicine, liquorice extracts are often used as a flavoring agent to mask bitter taste of preparations and also as modifiers of the cough reflex (Sofia and Walter, 2005). No attempt has yet been made to fully characterize phytochemicals present in the roots of this medicinal herb. Therefore, we sought to determine changes in the cough reflex after application of a water extracted polymeric fraction isolated from the *G. glabra* roots, which was defined as an arabinogalactan protein. *G. glabra* (batch MK018) was a generous gift from Divya Pharmacy (Haridwar, Uttarakhand, India). It contained 65% polysaccharides on the basis of fraction dry weight. Arabinose (52%) and galactose (22%) were the major neutral sugars together with the smaller amount of rhamnose (6%) and fucose (2%). The protein content was 210 mg/g of the fraction dry weight.

W. somnifera, the Indian equivalent to Ginseng (*Panax ginseng*), also known as Ashwagandha, is a plant from the *Solanaceae* family. This small evergreen shrub native to India, is commonly cultivated in the tropics and has been used in traditional Indian medicine for more than 2000 years mainly as an adaptogen (Kulkarni and Dhir, 2008). The plant lowers blood glucose in a manner comparable to that of an oral hypoglycaemic drug and increases urine volume, coupled with a decrease in serum cholesterol and triglycerides, with no adverse effects noted (Andallu and Radhika, 2000). The plant is also used in the treatment of infertility, carbuncles, ulcers, and painful swellings (Warrier et al., 1996). Moreover, it is the main component of a variety of formulations prescribed for common diseases of the respiratory tract (Kirtikar and Basu, 1935). Roots of the plant are the main sources of drug preparation. The decoction prepared from Ashwagandha is a viscous and highly polar solvent. In the experiments we used water extracted polysaccharide (acidic arabinan) of *W. somnifera* purified from the crude powder from roots. (Batch no, AL0054, Dabur India Ltd., New Delhi, India). It contained 65% sugars (arabinose 65% and galactose 18% out of the sugar content) and 22% proteins on the basis of fraction dry weight.

2.2. Animals

The study protocol was approved by the Ethics Committee of the Jessenius Faculty of Medicine, Comenius University in Martin, Slovakia (permission IRB 00005636). The experiments complied with the Slovakian and European Community regulations for the use and care of laboratory animals.

Adult conscious male TRIK strain guinea-pigs, weighing 200–350 g were supplied by the Department of Experimental Pharmacology, Slovak Academy of Science, Dobra Voda, Slovakia. They were kept in the faculty animal house with food and water *ad libitum* and with a standard air conditioning system. The animals underwent a week's quarantine before starting the experiment.

Polysaccharides from *A. vasica*, *W. somnifera*, and *G. glabra* as well as both control agents (positive control – codeine phosphate and negative – vehicle) were tested in individual groups of animals consisting of 8 guinea pigs each. Polysaccharides were given orally in a dose 50 mg/kg each. In the negative and positive control groups, 1 ml/kg water for injection and a solution of 10 mg/kg codeine phosphate were given orally.

2.3. Chemically-induced cough

The guinea-pig was placed in a body plethysmograph box (HSE type 855, Hugo Sachs Elektronik, Germany) and restricted, so that the head protruded into the head chamber and the neck was sealed with a soft diaphragm.

The cough reflex was induced by the aerosol of citric acid in a concentration 0.3 mol/l, generated by a jet nebulizer (PARI jet nebulizer, Paul Ritzau, Pari-Werk GmbH, Germany, output 5 l/s, particle mass median diameter of 1.2 µm), and delivered for 3 min to the head chamber of the plethysmograph. The intensity of the cough response was defined as the numbers of cough efforts counted during the 3 min exposure to the aerosol. The cough effort was defined as a sudden PC-recorded enhancement of expiratory flow associated with typical cough motion and sound observed by a trained staff.

The cough response was measured before administration of any agents (baseline measurement; *N* value in graphs) and then 0.5, 1, 2, and 5 h after their application. A minimal time interval between two measurements was 2 h to prevent animal's adaptation to the irritant, which could influence the response.

2.4. Specific airway resistance in vivo

Reactivity of airway smooth muscles *in vivo* was expressed as specific airway resistance calculated according Pennock et al. (1979). The value of specific airway resistance is proportional to the phase difference between nasal and thoracic respiratory airflows recorded in the head and thoracic chambers of the plethysmograph, respectively, which means that the bigger phase difference the higher the value of specific airway resistance and also a greater degree of bronchoconstriction.

2.5. Statistical elaboration

Data were presented as means ± SE. Changes in the number of citric acid-induced cough efforts and in specific airway resistance from baseline after the consecutive time intervals (0.5, 1, 2, and 5 h) elapsing from administration of compounds were evaluated with a *t*-test. *p* < 0.05 was considered to indicate a significant difference.

3. Results

Fig. 1 shows the effect on the cough reflex of polysaccharide compound from *A. vasica* (sample marked as P-601) extracted from the leaves and given orally in a dose of 50 mg/kg. There were

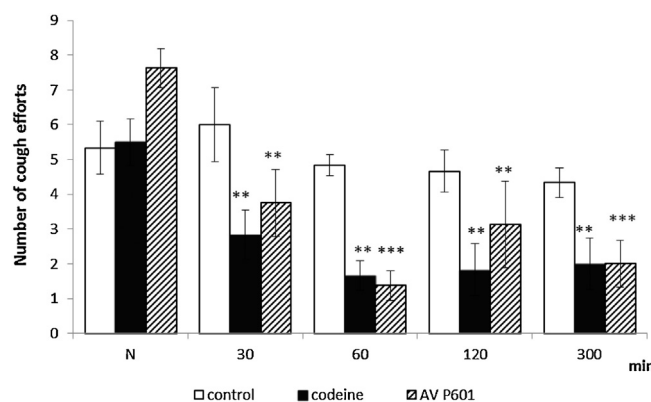


Fig. 1. Influence of water extracted polysaccharide P-601 from *Adhatoda vasica* (50 mg/kg) and codeine (10 mg/kg) on citric acid-induced cough in awake guinea pigs, recorded 30, 60, 120, and 300 min after oral application. *N*: initial values before application. Values are means ± SE; ****p* < 0.001; ***p* < 0.01; **p* < 0.05.

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