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Research Article

Anti-tussive, muco-suppressant and expectorant properties, and the safety profile of a hydro-ethanolic extract of *Scoparia dulcis*

George A. Koffuor[1]*, Jones Ofori-Amoah[1], Samuel Kyei[2], Stephen Antwi[1,3], Samuel Abokyi[2]

[1]Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, KNUST, Kumasi, Ghana, [2]Department of Optometry, School of Physical Sciences, University of Cape Coast, Cape Coast, Ghana, [3]Centre for Scientific Research into Plant Medicine, Mampong-Akuapem, Ghana

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***Correspondence to:**
George A. Koffuor,
Email: gkoffuor@yahoo.com

ABSTRACT

Background: *Scoparia dulcis* is used in Ghanaian folkloric medicine for the management of asthma and its related complications. This study was therefore aimed at evaluating the anti-tussive, muco-suppressant and expectorant properties of hydroethanolic extract of *S. dulcis* (SDE), and to ascertain its safety for use in asthma and obstructive pulmonary disease management.
Methods: The number of coughs induced in guinea pigs using citric acid and the concentration of phenol red secreted in tracheae of mice were measured. Preliminary phytochemical analysis was conducted on the extract using standard procedures. Safety for use of the extract was assessed by conducting an acute and delayed toxicity test.
Results: The extract showed a dose-independent inhibition ($p \leq 0.001$) of cough elicited by 7.5% citric acid, and a dose-dependent increase ($p \leq 0.05$) in the amount of phenol red output in mice tracheae similar to that of ammonium chloride. For the muco-suppressant activity, SDE dose-dependently reduced ($p \leq 0.001$) the concentration of ammonium chloride-induced phenol red secretions from mice tracheae. Phytochemical screening showed the presence of tannins, alkaloids, glycosides, saponins, steroids, and phenolic compounds. No acute and/or delayed toxic symptoms were observed after an oral administration of up to 5 g/kg of *S. dulcis* extract.
Conclusion: The results showed that *S. dulcis* extract has anti-tussive, muco-suppressant and, expectorant and/or mucolytic properties; making it a possible remedy for asthma, and obstructive pulmonary disease.

Keywords: Anti-asthmatic, Anti-tussive, Muco-suppressant, Expectorant, Obstructive pulmonary disease

INTRODUCTION

Asthma and chronic bronchitis are the common chronic inflammatory diseases of the respiratory tract, characterized by increased airway hyper-responsiveness and excessive mucus production. These lead to episodes of wheezing, coughing and shortness of breath.[1] As asthma progresses and persist, other factors such as edema, mucus hyper-secretion and the formation of inspissated mucus plugs, as well as structural changes of the airway smooth muscle, further limit airflow.[2]

Normally, mucus aids in the protection of the lungs in the human respiratory system, by trapping foreign particles that enter it during normal breathing. Mucus, furthermore, aids in moisturizing the inhaled air; and prevents tissues such as the tracheal and airway epithelia from drying out. The presence of mucus in the throat and/or trachea is usually normal, but increased quantities can impede comfortable breathing and have to be cleared by expectorating phlegm from the throat.[3] Consequently, increased mucus production in the respiratory tract is one common symptom of asthmatic reactions.

Cough is a physiological defense mechanism for the clearance of foreign materials and of excessive bronchial secretion in the airways.[4] It is one of the most common symptoms associated with pulmonary diseases such as asthma, bronchitis and chronic obstructive pulmonary disease (COPD). Hence, chronic cough is said to be a

symptomatic manifestation of airway hyper-responsiveness such as asthma.[5]

According to Adams et al.,[6] "Expectorant increases bronchial secretions and mucolytics help loosen thick bronchial secretions. Expectorants reduce the thickness or viscosity of bronchial secretions, thus increasing mucus flow easily through coughing; while mucolytics break down the chemical structure of mucus molecules, making the mucus thinner and can be removed more easily through coughing." An anti-tussive is a medicinal drug used in an attempt to treat coughing and related conditions. Currently available anti-tussives, such as codeine and dextromethorphan; though considered to be clinically effective, have sedative and addictive effects that limit their use.[7] There is, therefore, need to seek for an alternative remedy in the form of herbal plant formulations for anti-tussive, expectorant or mucolytic activities, and mucus-secretion suppression. One herbal plant that is deemed to be a panacea for all illness in traditional medicine is *Scoparia dulcis*.[8]

S. dulcis (Scrophulariaceae) is an erect perennial herb with serrated leaves producing white flowers, which grows to about half a meter in height; and is widely distributed in the tropical and subtropical regions. Phytochemical screenings of the herb revealed that it is rich in coumarins, phenols, saponins, tannins, amino acids, flavonoids, terpenoids and catecholamines. The pharmacological actions of *S. dulcis* are said to be due to the presence of these phytochemicals.[9-11]

The anti-tussive, mucosuppressant and expectorant properties of a hydro-ethanolic extract of *S. dulcis* (SDE), in addition to its safety concerns in usage, were thereby evaluated in this present study.

METHODS

Plant collection

The fresh aerial parts of *S. dulcis* was obtained between the months of July and September, 2013, from Osene-Adikanfo Herbal Centre, Mamponteng in the Ashanti Region of Ghana, identified and authenticated by the Herbal Medicine Department of the Faculty of Pharmacy and Pharmaceutical Sciences, KNUST, Ghana; where a voucher specimen (KNUST/HM1/2013/S027) has been kept.

Preparation of the hydro-SDE

The fresh aerial parts of *S. dulcis* was air-dried and milled into powder. One kilogram (1 kg) of the powder was macerated in 6.35 L of 70% ethanol for 72 hr. The suspension was filtered, and the ethanol evaporated off in a rotary evaporator (Rotavapor R-210, Buchi, Switzerland) and the concentrated extracts freeze-dried (Heto Power Dry LL3000, Jouan Nordic, Denmark) to obtain 27.65 g powdered material (percentage yield: 2.77%). The powdered material obtained, referred to in this study as the SDE was then stored at 4°C and reconstituted in a suitable vehicle for use.

Preliminary phytochemical analysis

Preliminary phytochemical analysis was then carried out on the plant extract according to the methods described by Sofowora[12] and, Trease and Evans,[13] to determine the groups of phytochemical constituents present.

Experimental animals

Male Dunkin Hartley guinea-pigs (220-320 g) used for the anti-tussive studies, BALB/c mice (13-20 g) of either sex used to determine the expectorant and mucus-secretion suppression properties, and Wistar rats used to assess the safety profile of SDE, were all obtained from the Animal Unit of the Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, KNUST. These animals were fed on standard rodent pellet diet obtained from the Ghana Agro Food Company (GAFCO) in Tema, Ghana, and allowed free access to drinking water *ad libitum*.

Drugs and chemicals

Phenol red and sodium chloride were obtained from BDH Chemicals Ltd, Poole, England; sodium hydroxide from Avondale, England; sodium cromoglycate (SCG) from Ashford Laboratory Ltd., Macau; ammonium chloride from Philip Harris, Hyde-Cheshire; citric acid from Fisons Scientific Equipment, Loughborough; dihydrocodeine (DHC) from Bristol Laboratories Ltd., UK; and salbutamol sulfate from Letap Pharmaceuticals, Accra, Ghana.

Dosing of drugs to experimental animals

Dosing of the plant extract was done based on its known traditional usage. Dosing was done once daily by gavage for 7 days (anti-tussive), 4 days (expectorant) and 1 day (mucosuppressant), at a volume of 1 ml/kg. Individual dose volumes were calculated based on the animal's most recent recorded body weight. The oral route of administration was used because it is the intended human exposure route.

Anti-tussive property of SDE

The anti-tussive property of SDE was studied using the citric acid-induced cough in guinea-pigs.[14] Guinea-pigs were kept in the experimental area of the departmental animal house at room temperature (26 ± 2°C), ambient relative humidity (65 ± 10%) and normal dark-light cycles, with food and water ad *libitum* for 10 days prior to experimentation. Guinea-pigs were then put into six groups (n = 6). Group one served as the normal control group and treated with distilled water alone; Groups 2 and 3 served as the positive control groups and, were treated with 10 mg/kg salbutamol per os and 20 mg/kg DHC

per os (reference comparators), respectively, whereas Groups 3-6 were treated with 50, 100, or 250 mg/kg of SDE orally.

The guinea-pigs were put into a Perspex box (20 × 12 × 14 cm) and exposed to a 7.5% citric acid aerosol (delivered by an ultrasonic nebulizer) for 5 min. During this period, the procedure was filmed, and the animals were continuously watched for cough reflexes. The number of coughs was counted (control basal value). After overnight fasting (with water ad *libitum*), the guinea-pigs were pre-treated with either SDE or reference drugs, 1 hr before re-exposure to the citric acid. Anti-tussive activity was then evaluated in each guinea-pig as the reduction in the number of coughs in comparison with the previously established control basal value.

Percentage Cough Suppression = [1 – (C2/C1)] × 100;

(where, C1 = control basal values, and C2 = total number of coughs after drugs administration).

The animals were then treated for 7 continuous days with the different assigned treatment regime, and the anti-tussive activity determined afterwards as described previously.

Muco-suppressant property of SDE

The muco-suppressant property of SDE was investigated using the ammonium chloride-induced phenol red secretion in tracheae of mice.[15] Mice were allotted to five different treatment groups (n = 6). Group 1 was kept as normal control. Group 2 (positive control) was pre-treated with 100 mg/kg SCG intraperitoneally for 15 min. Groups 3, 4, and 5 were pre-treated with 50, 100, and 250 mg/kg SDE orally for 30 min, respectively. Induction of mucus secretion was then carried out with 5 mg/kg ammonium chloride *per os*. Thirty minutes after ammonium chloride administration, animals were then injected with 500 mg/kg phenol red intraperitoneally. The trachea was excised from each mouse and cleared of adhering tissues, after sacrificing it by cervical dislocation, 30 min after the phenol red injection. Each excised trachea was then washed in 3 ml physiological saline, and sodium hydroxide (0.3 ml, 1 M) added to the washing to stabilize the pH of the lavage fluid. The absorbance of the mixture was then read at 460 nm using a spectrophotometer (T90 + UV/VIS Spectrometer – PG Instruments Ltd). A calibration curve for phenol red was determined; from which concentrations of phenol red secreted by mice tracheae were extrapolated.

Expectorant property of SDE

The expectorant activity of SDE was studied in vivo using the tracheal phenol red output in mice.[15,16] Mice were put into five groups (n = 6). Group 1 was kept as normal control. Group 2 (positive control) was treated with 1000 mg/kg ammonium chloride. Groups 3, 4, and 5 were treated with 50, 100, and 250 mg/kg of SDE *per os*, respectively. All groups were treated for 4 consecutive days. One hour after drugs administration on day 4, all animals were injected with 5% phenol red solution at a dose of 0.001 ml/kg, intraperitoneally. Animals were then sacrificed by cervical dislocation 30 min after the phenol red injection. The tracheae were, thereafter, removed and put into 1 ml normal saline immediately. These were then ultrasonicated for 15 min, after which 1 ml $NaHCO_3$ solution (5%, w/v) was added to the solution to stabilize the pH. The optical densities of the mixture were then measured at 558 nm using a spectrophotometer (T90 + UV/VIS Spectrometer – PG Instruments Ltd); and the concentrations of phenol red secreted by mice tracheae determined.

Safety studies

The complete acute testing method was employed; using healthy Wistar rats (140-160 g) of either sex. Rats were put into five groups (n = 6) and SDE administered orally at dose levels of 50, 100, 500, 1000, and 5000 mg/kg. The animals were observed closely for up to 24 hrs after drug administration for toxic symptoms (acute). They were observed further for up to 14 days for possible delayed toxicity, and the time of onset, intensity and duration of these symptoms recorded, if any.

Data analysis

Data obtained in all experiments were expressed as mean ± SEM. Statistical analyses were done by one-way analysis of variance (ANOVA) with Dunnett's Multiple Comparison test (*post hoc* test) using Graph-Pad Prism for Windows Version 5.0 (Graph-Pad Software, San Diego, CA, USA). Differences between means of treated groups and the control were regarded as statistically significant at $p \leq 0.05$.

RESULTS

Phytochemical screening

The preliminary phytochemical analysis of SDE showed the presence of tannins, alkaloids, phenols, glycosides, saponins and steroids, as shown in Table 1.

Anti-tussive property

SDE dose-independently inhibited the cough response induced by 7.5% citric acid significantly ($p \leq 0.001$). DHC also reduced the cough elicited significantly ($p \leq 0.001$). Salbutamol however did not show such significant effect ($p \leq 0.05$) on cough suppression as SDE and DHC. In further experiments, the effects of SDE and standard comparators over a repeated dosing period (7 days) were similar with those observed after a single treatment; with salbutamol showing no significant effect at all (Figure 1).

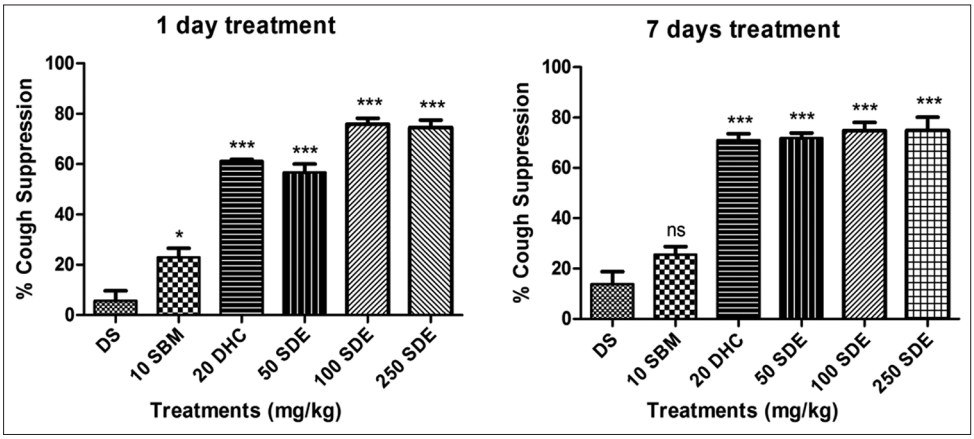

Figure 1: Percentage cough-inhibition by SDE, Dihydrocodeine, Salbutamol, and distilled water in citric acid-induced cough in guinea pigs after 1 and 7 days treatment. Values plotted are means ± SEM of n = 6. ns implies $p > 0.05$; * implies $p \leq 0.05$, * implies $p \leq 0.001$.**

Table 1: Phytochemical constituents of the ethanolic extract of *S. dulcis*.

Phytoconstituents	Tests	SDE
Saponins	Frothing test	+
Alkaloids	Dragendorff's test	+++
Tannins	Ferric chloride test	+
Steroids	Lieberman Burchard's	++
Triterpenoids	Salkowski test	−
Flavonoids	Shinoda test	−
Reducing sugars (General glycosides)	Fehling's test	++
Anthraquinones	Ammonia test	−
Phenols	Ferric chloride test	+++
Polyuronoids		−
Cyanogenic Glycosides		−

+: Present, −: Absent, SDE: Ethanolic extract of *S. dulcis*

Muco-suppressant property

The tracheal phenol red concentrations for all the treatment groups were found to be markedly lower ($p \leq 0.05$) than the controls (Figure 2). SDE also showed a dose-dependent reduction in the concentration of ammonium chloride-induced phenol red secretions from the mice tracheae, which were significantly ($p \leq 0.001$) different from the control. SCG reduced the amount of phenol red secreted significantly ($p \leq 0.001$); similar to the effect of the 250 mg/kg SDE.

Expectorant property

The concentrations of tracheal phenol red outputs for all the treatment groups were higher than that of the controls (Figure 3). SDE showed a dose-dependent increase in the amount of phenol red secreted in mice tracheae; with the 50 mg/kg dose given no significant effect. The positive control used (ammonium chloride) also increased the amount of tracheal phenol red secreted in mice significantly.

Acute and delayed toxicity studies

No mortality occurred during the study. Daily clinical observations recorded were considered common findings in laboratory rats, which could not be associated to SDE treatment. There were no secretions from the eye, ear, nose, anus and external genitalia, no "wasting", audible "chattering", alopecia, and pallor in the eyes. The mice were not lethargic, they fed well and had normal formed stool. There were no ocular findings, decreased motor activity and neurological conditions. There was also no significant test article effect on body weight.

DISCUSSION

Results from the study indicate that SDE has pharmacological effect as an anti-tussive, mucus secretion suppressant, and expectorant and/or mucolytic.

On exposure of the guinea-pigs to citric acid, cough reflexes were induced in the animals. Coughs can be recognized easily on the basis of sound associated with a rapid inspiration followed by a rapid expiration. Inhalation of a citric acid aerosol is known to cause cough in guinea-pig and man, and this response is said to involve sensory mechanisms. The cough reflex is triggered by the activation of rapidly adapting receptors (or 'irritant' receptors) within the larynx, trachea and the proximal bronchi, and of C-fiber endings found in the airway walls of the bronchi.[17,18] Afferent signals are transmitted through the sensory vagal fibers to the cough center, which has been experimentally identified as being in the region of the solitary nucleus in the medulla within the brain.[19] From the cough center, the impulses travel through the efferent pathways to the respiratory muscles (diaphragm, intercostal, and abdominal muscles) and the airways.[20]

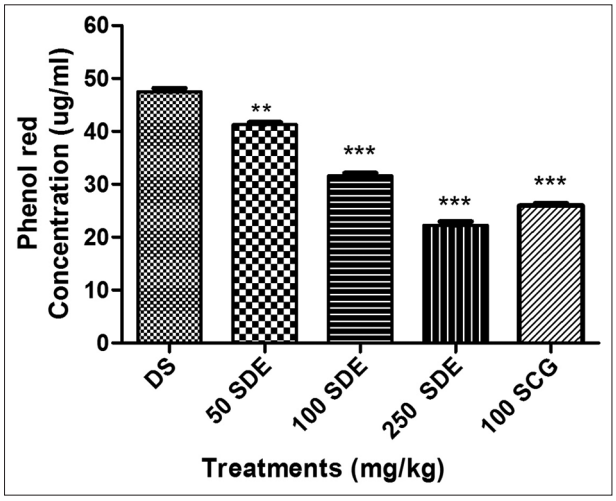

Figure 2: Effect of SDE, Sodium cromoglycate, and distilled water in ammonium chloride-induced phenol red secretions in tracheae of mice. Values plotted are means ± SEM of n = 6. ns implies p > 0.05; * implies p ≤ 0.05, * implies p ≤ 0.001.**

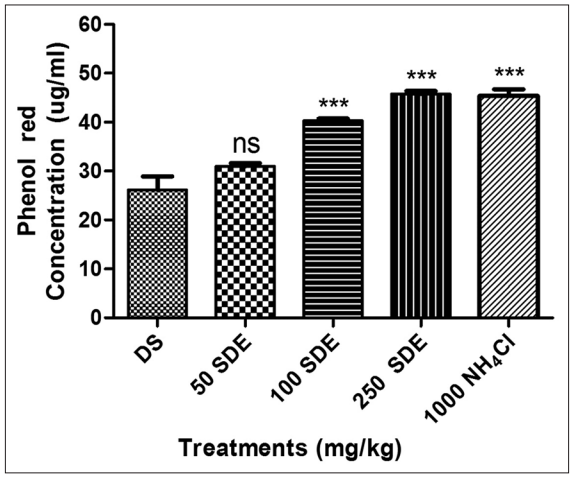

Figure 3: Effect of SDE, Ammonium chloride (NH_4Cl), and distilled water on the amount of tracheal phenol red outputs in mice. Values plotted are means ± SEM of n = 6. ns implies p > 0.05; * implies p ≤ 0.05, * implies p ≤ 0.001.**

SDE showed a dose-independent suppression of cough, comparable to that of DHC (Figure 1); and thus proved to be very potent in the inhibition of cough. DHC (similar in chemical structure and properties to codeine) is said to be a centrally acting anti-tussive, just as codeine, by depressing the cough centre.[7] Furthermore, other experimental studies have shown that codeine acts as well at the peripheral level. This was established as its anti-tussive effect was reversed by opiate antagonists with less penetration of the blood-brain barrier.[17] It is therefore possible that DHC may also be a peripherally acting opiate drug; by reducing the afferent fiber nerve inputs or inhibiting the activation of airway sensory receptors. It has however be noted that very few studies have attempted to clarify their mechanism of actions.[21]

Citric acid is also found to induce dyspnea, and this may depend on chemo-sensitive C-fibers afferents.[22] Cough and bronchoconstriction-induced by citric acid have been reported to have a clear dissociation.[23-25] These studies showed that SCG and atropine inhibited bronchoconstriction, but not citric acid-induced cough, whereas lidocaine and codeine inhibited cough but not bronchoconstriction. Subsequently, the inhibition of citric acid-induced cough by SDE was shown also to be independent of citric acid-induced bronchoconstriction. Here, different set of animals were pre-treated also with salbutamol, before the cough induction. Salbutamol did not show any significant level of cough inhibition induced by the citric acid (Figure 1). However, DHC and SDE were still efficient against cough induced by citric acid. The results affirmed the previous established fact that there is a diverging distinction between citric acid-induced cough and bronchoconstriction.

The extract showed a significant reduction on ammonium chloride-induced dye (phenol red) leakage in the tracheae of mice, a model of airway mucus hyper-secretion. This was similar to the effect of SCG (Figure 2). Koyama et al.[26] suggested that SCG is effective in reducing excessive airway mucus. SCG is known to prevent the release of inflammatory mediators, such as histamine from mast cells; and the inhibition of calcium influx and chloride channels, and thus helps prevent the release of preformed cytokines from inflammatory cells.[27]

During an asthma episode, inflamed airways react to allergen-triggers, which invariably lead to the narrowing of the airways and production of excess mucus; making it difficult to breathe and adversely coughing.[28] Excess mucus production in the bronchi and bronchioles (as may occur in asthma or bronchitis) may be treated with mucosuppressants, and/or anti-inflammatory medications as a means of reducing the airway inflammation that triggers mucus over-production. This could potentially improve airway clearance and thereby aid in normal and comfortable breathing, during asthmatic conditions. It is possible that the anti-asthmatic activity of SDE may reside in its reduction of airway mucus hyper-secretion, similar to SCG; and/or its ability to provide better inhibition of mucus secretion through its anti-inflammatory property.[29,30]

In the expectorant test *in vivo*, SDE extract enhanced phenol red output in the tracheae of mice, with ammonium chloride as positive expectorant (Figure 3). This indicated that the plant has an expectorant and/or mucolytic activity. Ammonium chloride is known to cause irritative action on the bronchial mucosa; leading to the production of excess fluid in the tracheobronchial airways for easier clearance of mucus.[31] The mode of action of SDE may therefore be related to its ability to increase secretion of tracheobronchial fluids, and then probably a decrease in the viscosity of mucus.

Moreover, mucolytics are known and prescribed in clinical cases to facilitate expectoration. They act by reducing

sputum viscosity and loosening mucus from the respiratory tract, thereby expectorating it. It is reported also that, in some patients with COPD and a chronic productive cough, mucolytics can reduce exacerbation.[6] For dry coughs, treatment with anti-tussives may be attempted to suppress the body's urge to cough; while in productive coughs (coughs that produce phlegm), treatment is instead with expectorants. In view of the above-stated observations, *S. dulcis* may prove to be a better remedy for productive coughs as the plant appears to possess both expectorant and mucolytic properties, in addition to its anti-tussive activity.

More so, the ability and potentiality of SDE to show both mucosuppressant and expectorant activities make it a better adjunct to the remedy and/or effective management of asthma, obstructive pulmonary disease and possibly chronic bronchitis.

Many researches on natural products chemistry have verified that saponins and alkaloids from herbs are effective for anti-asthmatic, anti-tussive and expectorant activities.[31-33] Moreover, *S. dulcis* plant is reported to have saponin and alkaloid constituents. In the study, phytochemical analysis showed that the SDE extract contains saponins and alkaloids. Hence, these pharmacological properties may be due to these phytochemical constituents present. However, it is very important to further separate the various chemical constituents, from the plant extract, being effective on the inhibition of cough and mucus, as well as increase of secretion output.

The toxicity studies showed no record of death, implying that the lethal dose was <5000 mg/kg when given as a single dose. The "no effect on the body and skin" observed suggests that SDE may not have any allergic or carcinogenic effect on the skin, and thus it may not cause hypersensitization and neurogenic inflammation. Allergic reactions and cutaneous neurogenic inflammation can result in hyperesthesia, pruritus and hyperplasia, and carcinomas which cause pain at the site of development, and results in rats scratching, licking, or biting their skin in response to the allergy.[34] As noted by Richardson and Vasko,[35] the animals tend not to sleep, they lose their fur and, they look debilitated and unkempt (an evidence of an underlying illness), and unhealthy.

The plant extract does not cause autonomic nervous system hypereflexia; because lacrimation, miosis, rhinorrhea, salivation, urination, defecation, and labored breathing (which are signs of muscarinic hyperactivity) were not seen. Observations also showed no CNS excitation or depression, muscle relaxation effects (noticed as a decrease in locomotory activity) as well as pain and inflammatory effects (realized as writhing, change in gait and body posture, and decreased locomotory activity). The extract did not seem to have any "wasting effect". There was no pallor in the eyes (symptom of anemia).

CONCLUSION

The present study indicated that the SDE has anti-tussive, muco-suppressant, expectorant and/or mucolytic properties. These positive effects help verify its anecdotal use in the management of asthma. The no observable adverse-effect level (NOAEL) was less than 5,000 mg/kg *per os*.

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Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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