Indian Journal of Pharmacy and Pharmacology 2022;9(1):58–66

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Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Original Research Article

Antitussive effect of *Celosia argentea* granule formulation on SO_2 gas-induced cough in experimental animals

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ARTICLE INFO

Article history:
Received 02-02-2022
Accepted 22-02-2022
Available online 23-03-2022

Keywords:
Antitussive
Cough
Suppression
Celosia argentea L.
Codeine sulphate and granules
Inhibition

ABSTRACT

Background: All over world cough is a common symptom in respiratory disease. When cough becomes severe, opioids act as a potent drug, but they have various side effects like sedation, constipation, etc. Therefore, there is a need to have an effective antitussive formulation, which doesn't have respiratory depressant activity. The present study was carried out to evaluate the antitussive activity of granules containing *Celosia argentea* extract using a cough model induced by Sulphur dioxide gas in experimental mice.

Materials and Methods: The antitussive effect of *Celosia argentea* granule formulation on SO_2 gas induced cough in experimental animals, which compared to standard codeine sulphate and the result was determined by statistical analysis.

Results: The antitussive activity of the granules tested in control, standard and test animal group respectively, it was compared to standard codeine sulphate (10, 15, 20 mg/kg body weight). Codeine sulphate as a standard drug for suppression of cough, act as potent antitussive agent, which produced 25.29%, 33.33%, 47.13% inhibition in cough at a dose of 10mg/kg, 15mg/kg and 20mg/kg respectively, whereas, codeine sulphate (20mg/kg) showed a maximum inhibition of 47.13% ($p<0.01$) after 60 min. of experiment. The test group of mice was showed 41.17%, inhibition, in cough on treatment with *Celosia argentea* granules after 60 min. of an experiment. This is very significant or nearly equal to a maximum dose of codeine sulphate (20mg/kg).

Conclusion: Statistical analysis shows very significant antitussive effects of *Celosia argentea* granules at the level of $p<0.01$ in inhibiting the cough reflex at 200 mg/kg body wt. in comparison to the control group.

1. Introduction

A *cough* , is also called as tussis, is a voluntary either involuntary carry through clear the throat as well as breathing passage of foreign particles, fluids, microbes, irritants, and mucus; it's a rapid expulsion of air from the lungs, it interferes with quality of life and even cause exhaustion. Cough is a forceful expulsion against a closed glottis which associates with typical noise. Most of all respiratory tract disorders result in induction of cough which require drug treatment for getting relief from cough. Induction of chronic cough may results in change in quality of patient's lifestyle.[1] Dry cough

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https://doi.org/10.18231/j.ijpp.2022.011

are related with eosinophilic bronchitis, irritation of airways due to several environmental pollutants, airway hypersensitivity due to infection, gastro esophageal reflux disease and also without any related cause, is mentioned to as idiopathic cough.[2] Rapidly adapting pulmonary stretch receptors (RARs) located in airways, initiate protective reflexes in response to a variety of stimuli, including large or rapid lung inflation or deflation, inhaled irritants, and, possibly, airway edema. Cigarette smoke activates RARs and elicits a cough to rid the airway of the offending material.[3,4]

Hydration of respiratory tract by steam inhalation, demulcents are adequate to decreasing symptoms in common of cases but, for uncontrolled cough, opioidergic central cough suppressants are more preferred. Among opioids, codeine, pholcodine, noscapine, dextromethorphan are potent, but they have certain constitutional side effects like sedation, constipation, as well as addiction liability. Also, their use in serious cough conditions like asthma is contraindicated, as they are known to more compromise the respiratory function. Currently, coughing can be alleviated with the use of drugs such as antitussives and expectorants such as codeine, theobromine (TB), and ambroxol (AM); however, treatment should encompass the underlying condition that induces the cough. The problem is more than just efficient therapy for coughing, as this will inevitably result in side effects.[5]

Hence, there is essential to have effective antitussive which can successfully improve chronic cough without side effects. Cough suppressant and anti-asthmatic activities have been claimed for many medicinal plants, in the literature. On the basis of this knowledge, different workers have assessed botanicals for antitussive/cough suppressant activity. For example Ocimum sanctum, Passiflora incarnates, Ionidium suffruticosam, Trichodesma indicum, Asparagus racemosus etc. While it is apparent that the different medicinal plants would work by different mechanisms of suppressing cough; there are very few studies available on the combined activity of the different medicinal plants.[6]

Celosia argentea is an erect annual herb up to 2 metres tall. The stem is ridged, glabrous and branches up to 25 per plant. The leaves are alternate, simple, without stipules; petiole indistinctly demarcated; blade ovate to lanceolate-oblong or narrowly linear, up to 15 centimetres x 7 centimetres, tapering at base, acute to obtuse and shortly mucronate at apex, entire, glabrous and pinnately veined. Inflorescence a dense, many flowered spike at first conical but becoming cylindrical up to 20 centimetres long, braceate, slivery to pink in ornamental forms completely or partly sterile and in many colours. Flowers are small, bisexual, regular five merous, tepal free, narrowly elliptical-oblong, 6-10 millimetres long, stamen fused at base, ovary superior, 1- celled, style filiform up to 7 millimetres long, stigma 2- 3,very short. Fruit is an ovoid to globose capsule 3-4 millimetres long circumscissile, few seeded with seeds being lenticular, 1- 1.5 millimetres long, black, shinning, shallowly reticulate.[7]

Celosia argentea is leafy herb commonly known as quail grass, feather cockscomb, and Lagos spinach belongs to the family Amaranthaceae. Plant show simple and spirally arranged leaves, flowers are often pinkish or white colour, fruits are in globular shape and seeds are black. Traditionally it is used for prophylaxes of various disorders like jaundice, inflammation, fever and itching. Blood disorders and mouth sores treated with the help of seeds of *Celosia argentea* which have bitter taste. They are effective remedy for diarrhea.[8] The *Celosia argentea* contains a variety of species some of them includes spicata, cristata, c. argentea. This is also known as kurdu. This is the earliest classical herb in China, and is frequently used in traditional Chinese medicine for treating eye diseases, ulcer, to serve as anthelminthic, to treat trauma to blood, hygro-paralysis etc.[7] The treatment with *Celosia argentea* also significantly improved the weight loss which was observed in diabetic rats by restoring the urinary glucose and protein release. Hypertriglyceridemia and hypercholesterolemia are the common lipid abnormalities in diabetes.[9] Based on ethno botanical practice the plant was investigated for anti inflammatory, anti — pyretic[10] anti diabetic,[11] anti bacterial and diuretic properties.[12] The stems and leaves bruised and applied as poultice is used for infected sores, wounds and skin eruptions.[13] Poultice of leaves, smeared in honey, is used as cooling application to inflamed areas and painful affections such as buboes and abscesses. Leave concussions are used to relieve gastrointestinal disorders and are antipyretic. Seeds when in decoction or finely powdered, are considered antidiarrhoeal or aphrodisiac. Whole plant is used for antidote in snake poison while root is used for abdominal colic, gonorrhea and eczema.[14] The seeds are prescribed for haemorrhagic conditions including menorrhagia, haematuria, haematemsis, haemoptysis, epistaxis, acute retinal heamorrhage and bleeding haemorrhoids.[15] *Celosia argentea* has sometimes been useful for treatment of disorders like excessive menstruation and leucorrhea. *Celosia argentea* is also used in traditional medicine for sores, ulcers, and skin eruptions.[16] Leave concussions are used to relieve gastrointestinal disorders and are antipyretic. Whole plant is used for antidote in snake poison while root is used for abdominal colic, gonorrhea and eczema. On the basis of this and on account of alleged usefulness of *Celosia argentea* in the traditional treatment this current study was aimed to investigate anti-tussive potential of the flavonoid fraction from alcoholic extract of the leaves of *Celosia argentea* in rodents.

2. Materials and Methods

2.1. Plant material

The plant was collected from the fields located in outskirt of Bharati Vidyapeeth, morewadi, Kolhapur. Routine pharmacognostic studies were carried out to confirm identity of material. The Plant was authenticated by the Botany Department (Shivaji, University, Kolhapur, and Maharashtra); Plant authentication voucher specimen number was (GGK-01).

2.2. Extraction of celosia argentea leaves

The leaves were shade dried and 1.5 kg coarsely powdered leaves were subjected to hot continuous extraction in soxhlet apparatus with methanol (95%). The extracts were concentrated and dried for further studies at reduced temperature and pressure in rotary evaporator. Yield obtained was 300 g (20%).[10]

2.3. Phytochemical screening of extract

The standard screening test was carried out for various plant constituents like Saponin, flavonoids, alkaloids, steroids, terpenoids, tannins, glycosides, carbohydrates, Proteins, Phenolic compounds and anthraquinones.[13]

2.4. UV-spectroscopy

The *Celosia argentea* extract were tested using UV-Spectroscopy to confirm the presence of phytochemicals in the sample with the help of standard UV-range (254nm) with the reference of literature.

2.5. Preparation of standard stock solution

The standard stock solutions of *Celosia argentea* extract was prepared by dissolving 10 mg of extract in Phosphate Buffer (pH 6.8): Ethanol in 70: 30 proportion and final volume were adjusted with the same solvent in 100mL of the volumetric flask to get a solution containing 100μg/ml. From the above solution concentrations of 10, 20, 30, 40 and 50μg/ml were prepared. Working standard solutions for each solvent were scanned at the selected wavelength and the calibration curves were constructed. The calibration curve for extract was plotted by taking absorbance at 254nm.[17]

2.6. Thin layer chromatography

The identification of phytoconstituents was carried out by using TLC. Different reported solvent systems and spraying reagents were tried for developing a TLC system for identification of constituents on the basis of a literature survey and phytochemical screening. The solvent system Toluene: Ethyl acetate: Formic acid (5:4:0.2)[10–18]

2.7. Formulation of granules

For the preparation of granules, the accurately weighed quantities of extract and other excipients were mixed together in mortar and pestle to form homogeneous powder blend, and by using wet granulation technique the formulation was optimized. The ingredient which used for granule formulation has been shown in Table 1.

Table 1: Ingredient of formulation

Sr. No.	Ingredients	Quantity
1	Extract	200mg
2	HPMC K 100	50mg
3	MCC 102	50mg
4	Talc	50mg
5	Mg St.	06mg

2.8. Evaluation of granules

2.8.1. Flow properties[19–23]

2.9. Bulk density

Apparent bulk density (ρb) was determined by pouring the powder blend into a graduated cylinder. The volume bulk (Vb) and weight of powder (M) were determined. The bulk density was calculated using the formula.

$$\rho b = \frac{M}{Vb}$$

2.10. Tapped density

The measuring cylinder containing a weighed amount of powder blend was tapped for a fixed time. The minimum volume (Vt) occupied by powder blend after a fixed number of toppings in the cylinder and weight (M) of the blend was measured. The tapped density (ρb) was calculated by using the following formula,

$$\rho b = \frac{M}{Vt}$$

2.11. Angle of repose

The flow ability of a powdered blend of all the batches was assessed by the angle of repose. The angle of repose was determined by using fixed funnel free-standing cone method. The angle of repose was determined in triplicate for all the batches by using the formula,

$$\theta = tan^{-1}\left(\frac{H}{R}\right)$$

Where 'θ'is angle of repose; 'H'is height between lower tip of the funnel and the base of a heap of powder; and 'R'is radius of the base of heap formed (Jadhav et al.; 2010).

Different ranges of flow ability in terms of angle of repose are given below

Table 2: Relationship between the angle of repose (θ) and flow properties

The angle of Repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2.12. Carr's compressibility index and hausner's ratio

Powdered Blend of all the batches were evaluated for Carr's compressibility index (CCI) and Hausner's ratio (HR). Bulk density apparatus was used for tapping (Lab Hosp, Mumbai, Maharashtra, India).

$$CCI = \frac{TD - BD}{TD} \; x \; 100$$

$$HR = \left(\frac{TD}{BD}\right)$$

Where, TD and BD have tapped density and bulk density respectively.

Table 3: Powders for their flow properties according to Carr's index

Consolidation Index (%)	Flow
5-12	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Very Very Poor

2.13. Moisture content

Control of moisture content in granulations is very important and it could affect the physical and chemical performance of final dosage forms. Moisture content is generally measured by moisture analyzer during product development; a thin layer of sample was heated at a set temperature until it reaches a constant weight and the results are expressed as LOD. The moisture in solid can be expressed as a wet weight or dry weight. On a wet weight basis, the water content of the material is calculated as % of the weight of wet solid, whereas dry weight basis the water is expressed as a percentage of the weight of dry solid. The measurement of moisture in wet solid is that calculated on a dry weight basis. This value is referred to as moisture content. The following formula used to calculate moisture content:

% Moisture content = (Weight of water in sample x 100) / Weight of dry sample

2.14. Experimental animals used

The experiment was carried out in Albino mice of either sex weighing between 30–40 g obtained from the animal house of Integral University. Animals are kept in the animal house at 26±2oC in polyacrylic cages with not more than six animals per cage and kept under standard laboratory conditions along with Standard food and water *ad libitum.*

The mice were used for the experiment after an acclimatization period of one week beforeexperimentation. Animals were divided into three groups; containing 3mice each. The animal experiment was performed according to ethical committee approval and guidelines BVCPK/CPCSE/IAEC/01/16/2020.

3. Evaluation of Antitussive Activity

3.1. Sulphur dioxide (SO2) induced Cough:[24]

Antitussive effect against sulfur dioxide-induced cough was evaluated by the method as described by Miyagoshi et al., 1986. The experimental model is shown in Figure 1, where V1 is 500 mL three-necked flask containing aqueous saturated solution of sodium hydrogen sulfite. By opening the stopcock of a burette V2, the concentrated sulfuric acid was introduced to generate sulfur dioxide gas. The chemical reaction that occurred in the flask A is:

$2NaHSO3 + H_2SO_4 = 2SO2 \uparrow + Na2SO4 + 2H2O$

Previously, SO_2 gas was filled in V1 and V3 gas reservoirs, and then by opening the cocks 3 and 2, pressure in the gas reservoir V3 was elevated which was recorded by the water manometer V4. Then the stopcock 2 was closed and stopcock 4 was opened slightly till the pressure in V4 (11 mm i.d.) reached 75 mm water, when the stopcock was closed. The procedure was operated in a draught. The mice were divided into five groups, each containing 6 mice. One group served as a control group receiving only 2% v/v aqueous Tween 80 solution (10 mL/kg, per orally). Three groups were used for standard drug i.e. Codeine sulphate 10 mg/kg, 15 mg/kg & 20 mg/kg respectively and the remaining group were used for test drug *Celosia argentea* in a dose of 200 mg/kg. Both the extract and codeine phosphate were suspended separately in 2% v/v aqueous tween 80 solution. Initially, the cough responses of all groups of animals were observed (0 min) by placing the animals individually in a desiccators V5. The cocks 3, 6 and 5 were opened in order and when the pressure in V4 became 0 mm of water; all the cocks were closed immediately. A certain amount of SO2 gas (5 ml which was kept constant throughout the experiment) was introduced in the desiccators in this way. After 1 min of introduction of the gas, the mice were taken out of the desiccators and the frequency of cough was observed for 5 min in an open-ended filter funnel with a stethoscope at the tip in which the mice were confined. In this way the frequency of cough was observed for all animal groups at 0 min (before the drug

administration) and at 30, 60, 90, 120 min interval (after the drug administration).

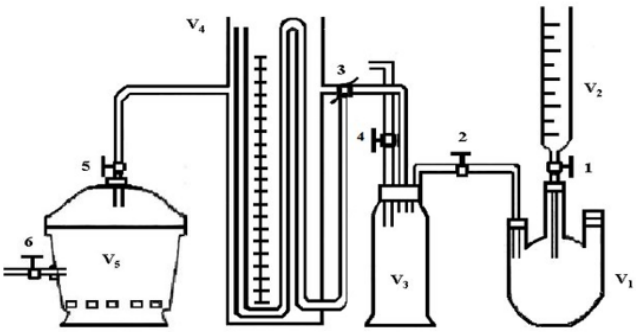

Fig. 1: Apparatus for antitussive evaluation by sulfur dioxide gas production. V1: Saturated NaHSO3 solution in 500 mL flask. V2: Concentrated H2SO4 in burette. V3: Gas cylinder. V4: Water manometer. V5:Desiccators

3.2. Statistical analysis

The frequency of cough produced by irritant-aerosol in animals was analyzed by one way ANOVA followed by Bonferroni's multiple comparison tests to compare all pairs of columns. The results are expressed as means ± standard error of mean (S.E.M.). The data obtained from sulfur dioxide induced experiment were analyzed by one-way ANOVA followed by Dunnett's test for comparing between the control group and the various groups. Statistical significance was assumed at the 0.05 levels.

4. Results and Discussion

4.1. Physical evaluation of extracts

The *Celosia argentea* extract was studied for physical evaluation by considering different parameters like color, odour, pH, percentage yield, melting point and nature of solid residue obtained after concentration of the extract. Extracts shows green colour with bitter odour and the pH was found to be 6.4. Melting point of extract shows within range of 120-130^{0}C, and the maximum % yield (11.10%) was found for water bath dried extract.

4.2. Phytochemical screening

Preliminary phytochemical investigation of *Celosia argentea* extract showed the presence of steroids, saponin, alkaloids, flavonoids, and glycosides

4.3. UV spectra of extracts

The UV spectroscopy analysis is important characterization of the drug by using wavelength maximum absorbance (λ max). The UV spectra of extract were in methanol. The λ max of extract *celosia argentea* extract was observed at 256nm which shows Figure 2.

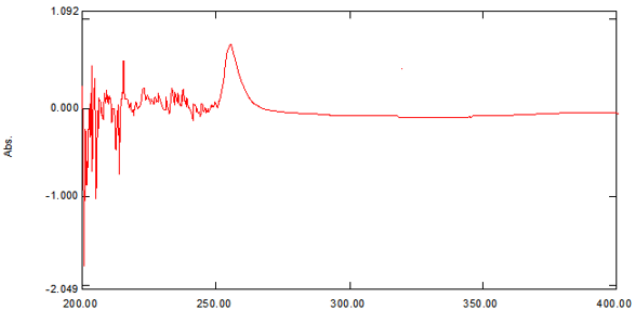

Fig. 2: UV spectra *Celosia argentea* extract

4.4. Calibration curve

The calibration curves of *Celosia argentea* extract were plotted in Phosphate Buffer (pH-6.8) by taking absorbance at 254nm

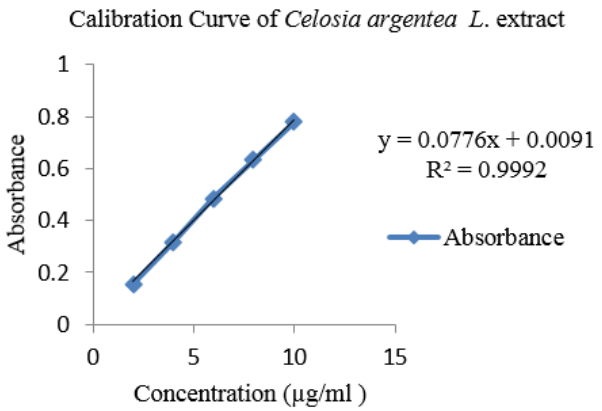

Fig. 3: Calibration *Celosia argente* extract

4.5. Thin layer chromatography (TLC)

TLC analysis was carried out by using different reported solvent systems for visualization of maximum spots on the TLC plate. The standard R_f value 0.75 was obtained by using Toluene: ethyl acetate: formic acid (5:4:0.2) solvent system.

4.6. Evaluation test of granules

The various flow properties of granules containing *Celosia argentea* extract was determined and summarized in Table 5.

Table 4: Flow properties of granules formulation batches

Formulation	Angle of Repose (θ)*	Bulk Density (gm/ml)*	Tapped Density (gm/ml)*	Compressibility Index (%)	Hausner's Ratio	Moisture content
Celosia argentea granules	31.54±0.3	0.673±0.14	0.886±0.21	24	1.316	2.5

n=3, ±sd

Fig. 4: TLC analysis of *Celosia argentea* extract

4.7. Standardization of cough induction model

With the reference of Gupta et al., 2009, evaluated the antitussive activity of formulations by using the method of Miyagoshi et al., 1986, with slight modification.[20,21] He specified that a vial containing 2 ml of 500 mg/ml solution of sodium hydrogen sulfite in double distilled water was placed at the base of a desiccator and covered with wire gauze to serve as a platform for placement of mice. To the NaHSO3 solution, 0.2 ml of sulfuric acid was added using a pipette. After 15 s, SO2 was exposed for 35 s in mice and was placed on the platform in the desiccator. Then, mice were removed from the desiccator and placed in an observation chamber for counting of bouts of cough for 5 min thereafter. However, in laboratory condition, when the mice were placed on the for counting of bouts of cough for 5 min thereafter, it produced too much cough, even on exposing for 35 s to SO2 gas show Table 6 and demonstrated in Figure 5.

The effect exhibited by the entire treated group on Sulphur-dioxide induced cough in experimental animals has been presented in

In normal controls, there was no significant change in the number of cough bouts, between the two exposures. The effect of the methanolic extracts of *Celosia argentea* on SO2 gas induced cough in experimental animals has significant effects at the level of $p<0.01$ in inhibiting the cough reflex

Table 5: Standardization of cough induction model in laboratory condition

Weight of animals(gm)	Exposure of SO2 gas(sec)	Frequency of cough bouts(In 5 min)
26	5	-
28	10	7
23	15	25
27	20	70
24	25	132
22	30	181
26	35	153

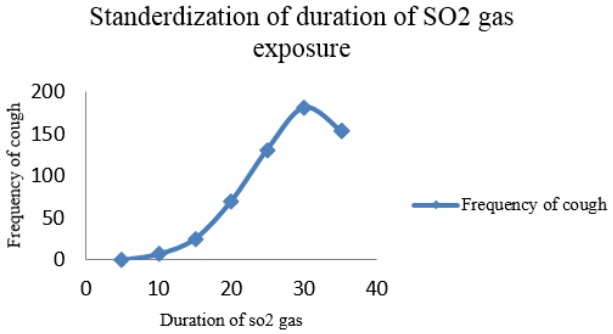

Fig. 5: Standardization of cough induction model in laboratory condition

Table 6: Effect exhibited by the entire treated group on sulphur dioxide induced cough in experimental animals

Effect of drugs and formulation on the cough reflex induced by SO2 gas in mice				
Treatment	**Dose (mg/kg)**	**No. of Animals**	**Frequency of cough (mean ± SEM)**	**Inhibition (%)**
Control group	–	1	87.66±5.31	–
Codeine sulphate	10	1	65.50±6.45 *	25.29%
	15	1	58.33±6.96	33.33%
	20	1	46.00±7.72 **	47.13%
Granules containing extract *Celosia argentea*	200	3	51.18±7.76 * #	41.17%

at a dose of 200 mg/kg body weight, in comparison with the control group.

Mice showed inhibition of 41.17%, in cough on treatment with *Celosia argentea.* Codeine sulphate used as a standard drug for suppression of cough, produced 25.29%, 33.33%, and 47.13% inhibition in cough at a dose of 10 mg/kg, 15 mg/kg and 20 mg/kg respectively**.** And codeine sulphate (20 mg/kg) showed a maximum of 47.13% ($p<0.001$) inhibition at 60 min of the experiment. The effect of the methanolic extracts of *Celosia argentea* on SO2 gas induced cough in experimental animals also have significant ($p<0.05$) effects in inhibiting the cough reflex at a dose of and 200 mg/kg body weight, in comparison with the Standard group.

The graphical representations of results have been shown in Figures 6, 7, 8 and 9

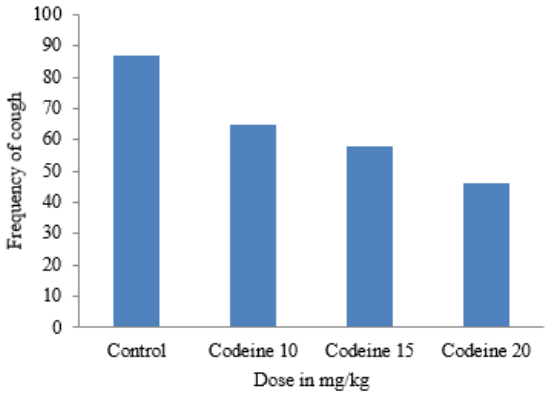

Fig. 6: Frequency of cough on treatment with codeine

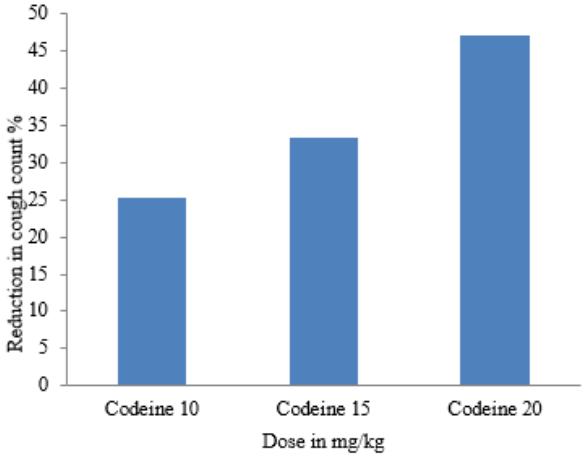

Fig. 7: Percent inhibitions in cough on treatment with codeine

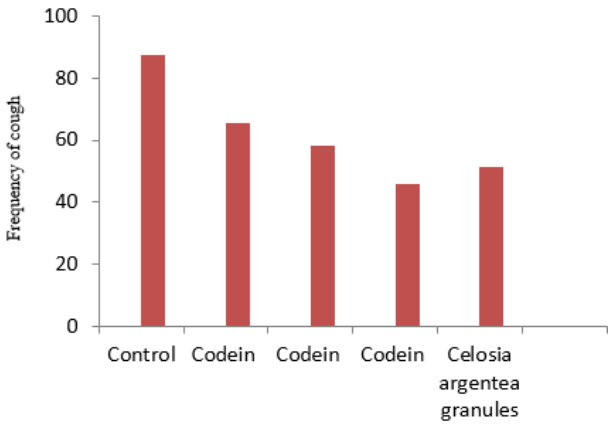

Fig. 8: Frequency of cough on treatment with codeine and *Celosea aurgentea* granules

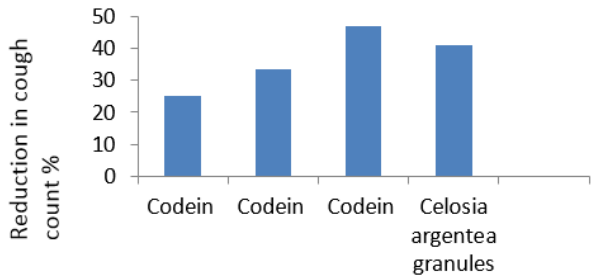

Fig. 9: Percent inhibitions in cough on treatment with codeine and *Celosea argentea* granules

Herbs are significant contributors to the quality of human life for thousands of years. It has been assessed by World Health Organization (WHO) that around 80% of world's inhabitants, mainly belong to in developing countries, rely on traditional medicine, and 85% of traditional medicine consists of the use of plant extracts or their active principles.[19,22] Various medicinal plants have been claimed to have antitussive activity. *For example-Ocimum sanctum, Ionidiumsuffruticosam, sparagusracemosus, Solanumxanthocarpum, ginger, etc.*[25–34] Worldwide main components of household cough and cold therapies, in the form of decoctions, teas, etc. *Celosea argentea* is an expectorant and demulcent in inflammation of bronchi tubules. The Celosian interferes with mucopolysaccharid synthesis as well as bronchial secretion or reduces its viscosity, facilitating its removal by coughing.

Some isolated experimental, as well as clinical studies, have been carried out on these agents for cough. The preliminary investigation indicated promising effects as an antitussive and expectorant activity, this aspect has been further investigated so that these herbs can be established individually as a standard antitussive and expectorant drug.

The model used in this study is a modification of Gupta, 2009. In this study, the quantification of SO2 generated has not been attempted, it is expected that the not only quantity but also saturation level in the chamber would be the similar in all the exposures, as the other conditions were kept the same. The present data indicates that the granules of extracts of *Celosea argentea* possess obvious antitussive activity against a chemically induced cough in mice. The antitussive activity of granules of the plant was tested and the results showed significant activity in this animal model which supports the use of the plant in traditional medicine. The granules at dose levels of 200mg/kg (*Celosea argentea* extract) showed significant activity after 1 h. as far as the frequency of cough as well as inhibition of cough reflex is concerned.

5. Conclusion

It can be concluded that the *Celosea argentea* extract containing granules have a significant antitussive effect in experimentally induced cough reflex in mice comparable to the standard drug codeine sulphate. The cough suppressant actvity of *Celosea argentea* was 47.13% as compared to the standard drug codeine sulphate. The difference between test drugs (*Celosea argentea*) and the control group was very significant at the level of $p<0.01$. And the difference between test drug (*Celosea argentea*) and standard group (codeine sulphate) was significant at the level of $p<0.05$.

6. Contribution of Authors

The authors have participated in the work including participation in the concept, design, analysis, writing, and revision of the manuscript.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Jadhav A, Tamboli FA, Chavan R, Thorat VH, Patil A, Jadhav S. Antitussive effect of *Celosia argentea* granule formulation on SO_2 gas-induced cough in experimental animals. *Indian J Pharm Pharmacol* 2022;9(1):58-66.