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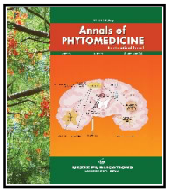

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Effect of polyherbal sugar free syrup on dry cough in experimental animal models

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Abstract

Evaluation of antitussive, antiallergic, and antihistaminic activity of polyherbal sugar-free syrup (Code Name: VASU-DC) for the treatment of dry cough using various models like compound 48/80 induced mast cell degranulation for antiallergic, citric acid induced dry cough for antitussive properties and *in vitro* spasmolytic activity for antihistaminic activity.

The acute oral toxicity was performed as per OECD 423 guidelines. Data are expressed as mean ± SEM and statistical significance was evaluated using the one-way ANOVA, followed by Tukey's multiple comparison tests.

Results of acute toxicity study of VASU-DC polyherbal sugar free syrup showed no signs of mortality or changes in clinical parameter. The polyherbal syrup significantly inhibits histamine induced contraction in goat trachea. VASU-DC syrup also protected the mast cells against compound 48/80 induced degranulation. The polyherbal syrup was also found to produce a dose dependent suppression of citric acid induced dry cough at the equivalent intended human doses in rats. VASU-DC at high dose produced maximum inhibitory effect (61.82%) and at low dose showed the minimum inhibitory effect (48.77%).

From the current study, it has been concluded that VASU-DC was found to be safe for 5000 mg/kg body weight. The components of VASU-DC having antitussive and antiasthmatic activity hence, VASU-DC has significant potential in the treatment of dry cough at the intended doses in *in vitro* and *in vivo* studies in rats. The data from present study confirms the beneficial effect of VASU-DC syrup in dry and allergic cough.

1. Introduction

An important natural defense mechanism of the respiratory tract is known as cough, which is a vital clinical sign for various non-respiratory and respiratory diseases (Mahashur, 2015). Coughing plays a significant role in a defensive reflex that enhances clearance of secretions and particulates from airways and also protects from aspiration of foreign particles like dust, pathogens (Polverino *et al.,* 2012). There are several causes of cough which may occur through a single causative factor or multiple causative factors includes airway disease, upper and lower respiratory tract infections, postnasal drip. Irritants like smoking, cardiac failure, airway obstruction, pulmonary edema, pneumonia, gastroesophageal reflux disorder (GERD), bronchitis, and environmental pollution (Keenleyside *et. al.,* 2006).

A dry cough may be a cough that does not remark mucous secretion. It is going to desire you have got a tickle within the back of your throat triggering your cough reflex, providing you with hacking coughs. It is also known as non-productive cough. Dry cough is usually troublesome to manage and may present in long fits. Dry coughs occur as a result of inflammation or irritation in your tract, however, there is no excess secretion to cough up. Currently, entire world facing pandemic coronavirus, the virus also exhibit preliminary symptom a dry cough (Chung *et al.,* 2008).

Respiratory tract disorders like post nasal drip syndrome, gastro esophageal reflex disorder, asthma, and other like environmental pollutants, smoking are also exhibiting dry cough as an important clinical feature (Irwin *et al.,* 2000; Galway *et al.,* 2019). There are several drugs like codeine, chlorpheniramine, antibiotics used in dry cough. However, these drugs have severe reported side effects like sedation, respiratory depression (Bedi *et al.,* 2020). Existing sugar free cough drops and syrup are incorporated with synthetic chemicals were also found harmful for oral dental hygiene (Mayo *et al.,* 2009).

The herbal medicinal plants used in treatment from very earliest period of human society. There are many evidences present which proven for the herbs getting from the plants are use in curing of many diseases, boosting healing process and use to achieve the mental and physical health. Herbs having significant role in nowadays as people affected by processing food, cigarette smoking, stress and over use of medicines. The plant vast potential to cure and treat the diseases and can be use as an alternative medicine for treatment along with this it is used to eliminate the side effect arise by the allopathic medicines (Malik *et al*., 2020; Biradar, 2015).

The treatment of dry cough herbal formulation use and limit the side effects arise form allopathic medicine. Despite of this fact

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limited sugar free polyherbal cough syrups are evaluated at preclinical stage. In present study, the VASU-DC polyherbal sugar free syrup consist of extract of the following medicinal plants mentioned in Table 1.

Table 1: Ingredients profile of polyherbal sugar-free syrup (Coded Name: VASU-DC)

Common name	Biological name	Parts used
Vasa	*Adhatoda vasica*	Leaves
Bharangi	*Clerodendrum serratum*	Root
Khatmi	*Althea officinalis*	Seeds
Haridra	*Curcurma longa*	Rhizome
Yashtimadhu	*Glycyrrhiza glabra*	Root
Tulsi	*Ocimum sanctum*	Aerial
Shati	*Hedychium spicatum*	Rhizome
Pippali	*Piper longum*	Fruit
Peppermint oil	*Mentha piperita*	Leaves
Cinnamon oil	*Cinnamomum zeylanicum*	Bark

Adhatoda vasica

Traditional uses (Hossain *et al.,* 2016)

Adhatoda vasica has been used from ancient times which gives a curative effect. According to ayurveda, the drug mainly acts on the respiratory tract. Various parts of the drug are used in asthma, cold, cough, eczema, joint pain, and malaria.

Clerodendrum serratum

Traditional uses (Gurav *et al.,* 2019)

Clerodendrum serratum is traditionally used in many diseases. Roots of *C.serratum* is used in asthma, rhinitis, cough, bronchitis, fever, inflammation, and dyspepsia. Aqueous leaves extract is used as a bronchodilator.

Althea officinalis

Traditional uses (Al-Snafi, 2013)

In the Unani system of medicine, the drug is used to treat inflammatory disorders like rhinitis, whooping cough, colitis, arthritis, and bronchitis. In ancient time, it is also used traditionally for the treatment of the irritation of oral, pharyngeal mucosa and associated dry cough, skin burns and for insect bites.

Curcurma longa

Traditional uses (Krup *et al.,* 2013; Naikodi *et al.,* 2021)

Turmeric is used from ancient time in Ayurveda, Siddha, and Unani systems of medicine. The meaning of haridra in sanskrit is 'an efficacious drug for jaundice'. The drug is used to treat cough and cold. Rhizome of turmeric is also given to cattle to treat stools.

Glycyrrhiza glabra

Traditional uses (Kaur *et al.,* 2013)

Glycyrrhiza glabra shows demulcent and expectorant activity. It is mainly used as a plating agent for bitter drugs in pharmaceutical formula-tions, such as quinine, aloe, ammonium chloride, *etc*. The glycyrrhetinic acid exerts mineralocorticoid activity, and hence it is used in the treatment of inflammations, rheumatoid arthritis, and Addison's disease. In anemia, powder of yasthimadhu is prescribed with honey. For promoting lactation yasthimadhu powder is mixed with cow's milk.

Ocimum sanctum

Traditional uses (Pandey and Madhuri, 2010)

Tulsi is also known as the 'Elixir of life'. Different parts of plants are used in several diseases to cure. It is used in cold, cough, influenza, asthma, sore throat, bronchitis, ulcer and arthritis, and migraine headaches. Leaves are also used to sharpen memory. It also helps to kill germs. Recent studies show anticancer activity.

Hedychium spicatum

Traditional uses (Rasool and Maqbool, 2019, Fahim M *et al.,* 2017)

The rhizomes are white and are used in the Holi festival. They are also used in vanishing cream and gives significant analgesic, anti-inflammatory activity. They are considered to have insect-repelling properties. It acts as an antidote for snake bites and is also used in malaria. Powdered rhizome is used in asthma, bronchitis, cough, and chest pain.

Piper longum

Traditional uses (Zaveri *et al.,* 2010)

The drug is used as an antidote in snake and scorpion biting. The ripe fruit is sweet, pungent which is used in laxative, anti-dysenteric, asthma, bronchitis, fever, urinary discharge, inflammation.

Mentha piperita

Traditional uses (Trevisan *et al.,* 2017; Gheorghe *et al.,* 2018)

Traditionally, it uses in the digestive disorders, treatment of cough, and immunostimulant.

Cinnamomum zeylanicum

Traditional uses (Saeed *et al.,* 2018)

Cinnamon has been used as a flavouring and flavour-enhancing food additive. It is also used as for treatment for oral infections and as a gastroprotective, Neuroprotective, cardioprotective and hepatoprotective properties. It is also recommended for nausea, vomiting, and in diarrhea.

Each of above ingredients is reported to have direct or indirect antitussive, antiallergic and soothing activity however no scientific evidences were available to prove safety and antitussive activity of their combination. The formulation may also use by diabetic patients as it is sugar-free syrup. Thus, the syrup is expected to produce a significant relief in dry cough.

Hence, the present study was carried out to evaluate acute toxicity, antitussive, antiallergic and anti-histaminic activity of selected polyherbal sugar free syrup.

2. Materials and Methods

2.1 Animals

In the experiment, wistar male rats (8-12 weeks) were used. With a 12-hour light-dark cycle, they were kept at a consistent tempera-

ture. The animals are feed with food and water *ad libitum*. Before the trial, the animals were given a week to acclimatize. The experiment was approved by IAEC and its protocol number is ROFEL/IAEC/2021/0001.

2.2 Drugs

Standard drug Benadryl-DC procure from the Rajvi Medical near Haria Hospital, Vapi, Gujarat and test drug VASU-DC received from Vasu Research Center, Makarpura, Vadodara, Gujarat.

2.3 Acute toxicity study

According to OECD 423 guidelines, the acute oral toxicity of the formulation VASU-DC polyherbal syrup was evaluated in healthy albino wistar rats. All animals were observed for the change in body weight, clinical signs and mortality especially for first four hour after the dose administration of the drug and subsequently twice a day during 14 days of time period (OECD Guidline, 2001).

2.4 *In vitro* spasmolytic activity

As per the experimental requirement, goat trachea was collected from slaughter house and organ bath preparation was done. After mounting the goat trachea, it was stabilize for 45 min. After the stabilization of preparation, the histamine responses are taken and recorded. After that, the response of histamine was taken with standard and test syrup as antagonist at each dose. The height of contraction of histamine is compared with height of contraction of histamine with antagonist. % relaxation was calculated by given formula:

% relaxation= 100−{height of contraction after exposure to antagonist /height of contraction before exposure to antagonist} * 100]

2.5 Antitussive activity on citric acid induced dry cough model (Ashwini *et al*., 2012)

The experiment was performed on male wistar rat weighing between 250-300 g. Citric acid is used as an irritant which was administered by spraying the citric acid solution (17.5% W/V) through the inhalation route in the histamine chamber. It was exposed for 15 sec. After exposure, the number of cough bouts produced by the animals was counted before drug administration as pre-treatment for 20 min and after one hour, the test substance was administered *via* oral route. After 30 min rest period, the rats were again re-exposed to the solution of citric acid for 15 sec, followed by 20 min observation as post-treatment. All the drugs were administered orally and divided into four groups (n=6). Each animal was served as its own control group before and after the drug administration.

Selected rats were divided into four groups each containing six animals. Group I served as disease control, Group II served as standard which was treated with benadryl DC and groups III and IV served as low dose and high dose of test syrup (VASU-DC) with 0.5 ml/kg and 1 ml/kg, twice a day, p.o., respectively. To avoid bias by the observer, the counting of bouts was done independently by two observers. The bouts were counted by using counters and stopwatches. The reading was accounted, only if the difference in the count is less than 10%. The mean of the two observations is taken as reading.

2.6 Mast cell degranulation (Krup *et al.*, 2013)

In this method, the mast cell will be extracted from the peritoneum of young healthy wistar rats. The rat's peritoneal cavity was injected with the 10 ml tyrode solution containing 5 IU/ml heparin and 0.1% bovine serum albumin. After gently massaging for 1-2 min. the injected fluid is collected. The collected fluid will be then subjected to centrifugation at 600 rpm for 10 min at temperature 4°C. After centrifugation, supernatant will be disposed of and the pellet containing mast cells will be washed with tyrode's solution and resuspended in tyrode's solution containing media. The solution will be transferred to test tubes. These test tubes are then subjected for incubation for 5 min at 37°C in the incubator. Five test tubes were taken. Test tube I as control in which only distilled water was added with mast cell suspension, Test tube II as disease control, where compound 48/80 was added, Test tube III as standard which was treated with sodium cromoglycate and Groups IV and V served as low dose and high dose of test syrup (VASU-DC), respectively.

2.7 Statistical analysis

All continuous data was analyzed using one-way-ANOVA, followed by Tukey's test and a value of $p<0.05$ was considered as significant.

3. Results

3.1 Acute toxicity study

The study of VASU-DC sugar free syrup was performed by using the reference of paragraphs 22 and 23 of OECD guidelines 423 limit dose study was done up to 5000 mg/kg in rats. The study's findings revealed that there were no indicators of mortality or clinical changes seen during acute toxicity studies.

Table 2: Observation for acute toxicity study at 5000 mg/kg dose

Parameters	Results
Body weight	No significant increase or decrease
Behavioural change	No change observed
General awareness	Normal
Clinical signs	No significant abnormalities observed
Autonomic symptoms	Normal

3.2 *In vitro* spasmolytic activity

In vitro spasmolytic effect of VASU-DC sugar syrup was determined using 10 times diluted solution of syrup. Histamine was taken in control, where 51 mm is taken as 100% height of contraction. Standard syrup reduces height of contraction when syrup is given with histamine which shows significant reduction as the dose of syrup increases. The height of contraction of histamine is compared with the height of contraction of histamine with standard and test as antagonist at each dose. VASU-DC test syrup shows significant reduction in height of contraction when given with histamine. As the dose increases, height of contraction reduces which shows significant to control group. This reduction in height of contraction shows the present of antihistaminic activity. Percentage of relaxation is shown in Table 3.

Table 3: Relaxant effect of formulation on isolated goat trachea

S. No.	Dose (ml)	Control group contraction	VASU-DC (Test)%relaxation	Benadryl-DC (Standard) %relaxation
1.	0.1	58.82%	20% *	31.66% *
2.	0.3	64.7%	24.24% *	36.36% *
3.	0.6	82.35%	33.33% *	42.85% *
4.	0.9	100%	44.11% *	51.96% *

All data are expressed as mean ± SEM and analysed by one-way ANOVA, followed by Tukey's test (multiple comparison) using GraphPad Prism.* $p<0.05$, when compared with control.

3.3 Antitussive activity on citric acid induced dry cough model

The antitussive activity of VASU-DC syrup was evaluated on cough bouts produced by citric acid solution. In this study, the effect of standard and test formulation on the number of cough bouts produced was compared. The frequency of cough bouts in control group who is receiving only citric acid in post-treatment was considered to be base value. Treatment with Benadryl-DC syrup (standard group) in post-treatment was found to reduce the frequency of cough bouts in the 20 min observation period, following citric acid exposure. The test syrup VASU-DC significantly inhibit the citric acid induced dry cough ($p<0.05$). High dose of VASU-DC syrup (2 ml) produced maximum inhibitory effect (61.82%) and low dose (1 ml) shows minimum inhibitory effect (48.77%). The number of cough bouts as well as % inhibition of dry cough induced by citric acid has been shown in table 4.

Figure 1: Citric acid induced dry cough.

Table 4: Effect of formulation on citric acid induced dry cough

Group	Dose (ml)	Frequency of dry cough (mean ± SEM)		% inhibition
		Pre-treatment	Post-treatment	
Control	1 ml/kg, p.o.	42.16 ± 1.42	39.16 ± 1.74	-
Standard- Benadryl-DC	2 ml/kg, p.o.	30.33 ± 1.64	23.33 ± 1.52	76.92 % *
Low dose of VASU-DC	1 ml/kg, p.o.	27.33 ± 1.52	13.33 ± 1.11	48.77 % *
High dose of VASU-DC	2 ml/kg, p.o.	25.33 ± 2.38	15.66 ± 1.38	61.82 % * #

All data are expressed as mean ± SEM and analysed by one-way ANOVA, followed by Tukey's test (multiple comparison) using GraphPad Prism.* $p<0.05$, when compared with control, # $p<0.05$, when compared with Benadryl-DC (standard).

3.4 Mast cell degranulation

The antiallergic activity of VASU-DC was evaluated using compound 48/80 induced mast cell degranulation. The mast cells were collected from rat peritoneum as described in method. The mast cell suspensions were used in four groups. The control group which only consist of mast cell suspension. Disease control group consist of mast cell suspension with compound 48/80. The other groups are test syrup, *i.e.*, VASU-DC and standard (sodium cromoglycate).The number of intact cells was calculated out of total of 100 cells in the field. In the control group, 77.83% cells were intact which was then incubated with compound 48/80 resulted in degranulation and number of intact cells was significantly reduced to 25.66 ± 1.11% (p<0.05). Sodium cromoglycate was taken as a standard and it inhibited the degranulation resulting in the intact mast cells to increase to 61.33 ± 1.17% (p<0.05). Test syrup VASU-DC (low dose) also protected the mast cells against compound 48/80 induced degranulation which was found to be 33.5 ± 1.83% (p<0.05) and high dose of syrup with maximum percentage intact mast cells was found to be 51.83 ± 1.15% (p<0.05). Antiallergic activity was shown in Table 5.

Table 5: Effect of formulation on compound 48/80 induced mast cell degranulation

Groups	No. of mast cells intact	No. of mast cells degranulated	% Intact mast cells
Control	77.83	17.33	77.83 ± 0.90
Disease control	25.66	65.16	25.66 ± 1.11 *
Standard	61.33	32.16	61.33 ± 1.17 *#
VASU-DC (Low)	33.5	24.66	33.5 ± 1.83 *#$
VASU-DC (High)	51.83	40.33	51.83 ± 1.15 *#$

All data are expressed as mean ± SEM and analysed by one-way ANOVA, followed by Tukey's test (multiple comparison) using GraphPad Prism.* p<0.05, when compared with control, # p<0.05, when compared with Benadryl-DC (standard). Where* p<0.05, when compared with control, # p<0.05, when compared with disease control, $ p<0.05, when compared with Benadryl-DC (Standard).

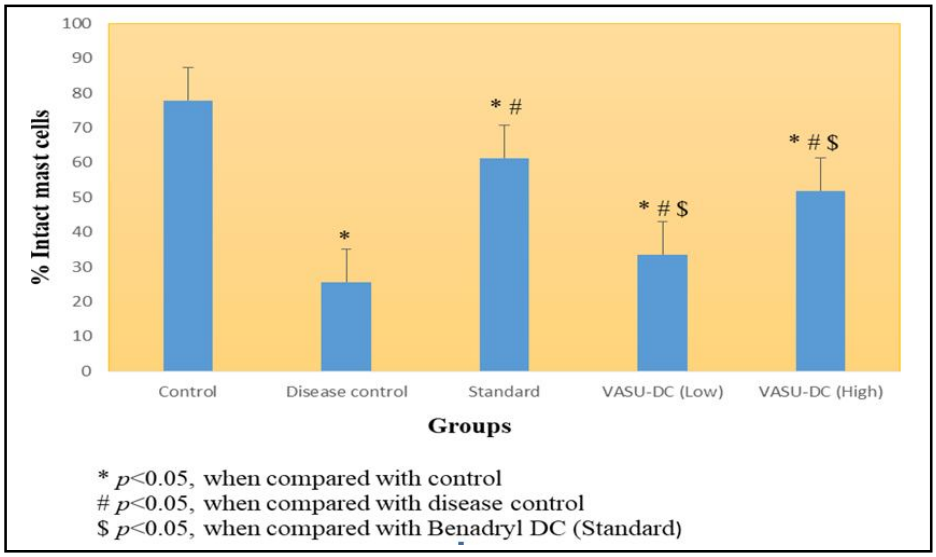

Figure 2: Inhibitory effect of syrup on compound 48/80 induced mast cell degranulation.

5. Discussion

Polyherbal sugar free syrup VASU-DC is a polyherbal formulation which consists of multiple herbs with different pharmacological activities. In the present study, the formulation consists of vital ingredients which contribute to different mechanism and provide relief from dry cough. Polyherbal formulation VASU-DC is sugar free syrup which exhibited significant relaxant effect in the presence of histamine on goat trachea. This effect is thought to be due to component like Haridra (Krup *et al*., 2013) and *Mentha piperita* (Trevisan *et al*., 2017) and may be responsible for their beneficial action in relieving cough. Further, Yasthimadhu (Al-Snafi, 2018), Shati (Rasool *et al.,* 2019) and Bharangi (Prasad *et al*., 2009) are also reported to mast cell stabilizing effect which was confirmed by evaluating VASU-DC syrup against compound 48/80 induced mast cell degranulation. This action is thought to produce antiallergic effect of the syrup.

The antitussive activity was evaluated by citric acid induced dry cough which shows significant antitussive action and the effect was found due to Khatmi (Al-Snafi, 2013), Vasaka (Hossain *et al.,* 2016) and Tulsi (Pandey *et al.,* 2010). The above results validate the use of VASU-DC, polyherbal sugar free syrup investigated in the present study for dry and allergic cough.

6. Conclusion

Polyherbal sugar free syrup VASU-DC was found to be safe and has significant potential in the treatment of dry and allergic cough at the intended doses in *in vitro* and *in vivo* studies in rats. The data from present study validate the beneficial effect of VASU-DC syrup in dry

and allergic cough. This sugar-free syrup might be a preferential formulation for diabetic patients. The sugar-free and polyherbal syrup might become a preferential option for children considering their oral hygiene needs

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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