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Original Article

Evaluation of Diuretic and Laxative Potential of *Onosma bracteata* Wall.: A Species of the Controversial Drug 'Gojihva'

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ABSTRACT

Background: *Gojihva* or *Gaozaban*, an Ayurvedic cum Unani Medicinal plant described with various properties, including diuretic activity. *Onosma bracteata* Wall. is considered the official species of *Gojihva* in Ayurveda and is one of the species considered Unani *Gaozaban*. **Materials and Methods:** The plant was subjected to physicochemical evaluation, sequential extraction, HPTLC profiling, and phytochemical screening. The diuretic and laxative activity of sequential methanol and water extracts of *O. bracteata* Wall. at a dose of 100 mg/kg and 200 mg/kg of body weight *per oral* was measured in Wistar rats in two separate experiments. **Results:** Preliminary phytochemical investigation and TLC profiling revealed the presence of flavonoids/hydroquinone/phenolics in methanol extract. Additionally, elemental analysis of plant material detected Potassium (K) at a level of 672.12 ppm. The methanol extract at doses 100 mg/kg (1.65 mL ± 0.19) and 200 mg/kg (2.00 mL ± 0.28) and aqueous extract at dose 200 mg/kg (1.63 ± 0.12) showed highly significant diuretic activity ($p<0.0001$) at 6 h compared to standard (0.67 mL ± 0.21). Whereas the aqueous extract of the plant showed mild constipation action. **Conclusion:** The literature search revealed that the diuretic potential of the methanolic extract could be attributed majorly to carbonic anhydrase inhibitory activity of constituent compounds like caffeic acid, rosmarinic acid, p-hydroxybenzoic acid, artitrichin, salvianolic acid, and coumarins, in addition to natriuretic, Ca^{2+} sparing activity, and increased renal excretory function. The milder diuretic action of the aqueous extract can be due to the presence of potassium salts in aqueous extracts. Thus, the traditional use of *Gojihva* as a diuretic is established on a phytochemical basis. Further pharmacological and phytochemical investigations of Methanol extract may reveal novel compounds with diuretic potential.

Keywords: Ayurveda, Carbonic Anhydrase, Gojihva, Gaozaban, Phenolics, Unani.

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INTRODUCTION

Onosma bracteata Wall. (Fam. Boraginaceae) is a perennial and hirsute or hispid herb. It is sparsely distributed in North-Western Himalayas from Swat to the Kumaon region at altitudes of 3,500-4,500 m. *O. bracteata* Wall. is officially considered Ayurvedic plant *Gojihva* out of 6 species being used and also one of the species which are considered as a Unani plant *Gaozaban*. *O. bracteata* Wall. is widely considered *Gojihva* in commercial medicinal plant markets and herbal industries in India. *O. bracteata* Wall. is commonly known as *Gojihva*, *Darvipatra, Kharparni* in Sanskrit, *Gaozaban* in Urdu, *Gaujaban, Gojiya* in Hindi, *Galjibhi*, *Bhonpathari* in Gujarati, and similar names in other local languages.[1–5]

According to ancient texts, the *Gojihva* has cardiotonic, antidiabetic, cough relieving activity, treatment of fever, absorbent, anti-asthmatic, antitoxic, beneficial for dental health, anti-inflammatory, wound healing, blood purifier anti-leprosy, and diuretic properties.[4,6] The plant is anti-asthmatic,[7] hepatoprotective,[8] anticancer,[9-10] anxiolytic,[11] cardiac and smooth muscle relaxant,[12] antiageing,[13] and heavy metal absorbent[14] as per various pharmacological studies. The plant contains novel phytochemicals with anti-aging properties such as Ehretiquinones B–D, Allomicrophyllone, and Ehretiquinone, which belong to the benzoquinones class of compounds.[13] Pulmonarioside C, 9′-methoxyl salvianolic acid R, and (-)-4-O-(E)-p-coumaroyl-L-threonic acid methyl ester are three new compounds isolated from the plant. Along with these, 34 compounds belonging to classes of coumarins, caffeic acid derivatives, p-hydroxybenzoic acid analogs, lignans, and glycosides thereof, have been reported from the plant for the first time.[15]

The plant's aerial parts reportedly have very high ash values, up to 26 %, and acid insoluble ash up to 4 %, per Ayurvedic Pharmacopoeia of India values. Elemental analysis of aerial parts showed presence of minerals such as Ca (36.3 %), K (22.3%), Mg (4.7%), Na (3.1%), S (1.4%), Fe (0.7%), P (0.4%), Zn (0.033%).[16]

Gojihva has diuretic properties as per ancient texts. Additionally, *O. bracteata* Wall. is one of the constituents of Cystone®, a polyherbal formulation by Himalaya Drug Company widely indicated for urinary stones and related diseases. Still, no diuretic activity has been reported for the plant individually. Thus, the authors explored the diuretic and laxative potential of the plant.

MATERIALS AND METHODS

Plant Material Physicochemical Evaluation and Extraction

Onosma bracteata Wall., whole plant coarse powdered (5 kg), was procured from Dishant Ayurvedic Suppliers, Ahmedabad. The origin of plant material is India. The Institute of P. G. Teaching and Research in Ayurved Pharmacognosy Lab, Gujarat Ayurved University, Jamnagar, Gujarat, India, authenticated the plant.

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The plant material was evaluated for physicochemical parameters such as ash content, alcohol extractable matter, loss on drying, swelling index, and foaming index as per WHO guidelines for Quality standards of Herbal Products.[17]

The successive extracts of petroleum ether, chloroform, and methanol extracts from 500 g plant material were prepared using the hot maceration technique with a temperature not exceeding 45°C. The 25 g of the remaining marc after successive extraction was subjected to maceration at 45°C for 24 hr in demineralized water with 500 mL water. The pooled extracts were concentrated using a rotary vacuum evaporator and dried in a vacuum oven.

TLC Profiling

HPTLC system with ATS4 – Autosampler, ADC – Automatic Development Chamber, Photovisualizer – Photo documentation, CAMAG derivatizer (CAMAG, Switzerland) was used for the HPTLC fingerprinting. HPTLC Silica Gel 60 F245 plates (Merck) were used for TLC development. All the solvents used were of AR grade. The HPTLC profile of methanol extract was developed and optimized using mixtures of various solvents as mobile phases. The TLC plates were run using an optimized mobile phase and then derivatized with different spray reagents to estimate the class of compounds.

Elemental Analysis

ICP OES (Inductively coupled plasma - optical emission spectrometry), Thermo Scientific, Model - iCAP 7000 Series was used to determine plant material elemental composition. Stock Standards 50 ppm (Merck) were used for the linearity plot. Linearity plot was done for 1, 2, and 3 ppm solutions of standards prepared by dilution of stock. 1 g of the plant material was mixed with 10 mL of HCl and 10 mL of HNO_3 in a beaker. The sample was digested using a hot plate. After digestion, volume was made up to 50 mL using a volumetric flask and filtered with Whatman ashless filter paper. The samples were run on ICP OES to determine elemental composition.

Diuretic Activity

Institutional Animal Ethics Committee of School of Pharmacy, R K University approved the diuretic and laxative activity protocol, vide proposal no. RKCP/COI/RA/21/107.

The diuretic activity was evaluated as per Mondal *et al.*[18] Wistar rats of either sex, weighing 200/220g, were divided into six groups of six animals each. Before experimentation, the animals were assessed for any disease indication, and only the healthy animals were chosen for the study. The study was carried out at a normal room temperature (25 ± 2°C). Before administering the extract/controls, the rat's bladder was emptied by gentle compression of the pelvic area and pulling of tails. Due to ease of administration and freedom to administer a large volume of fluids, the oral route was used to administer extract/controls. Group I (the control group) received 10 mL/kg of normal saline, Group II (the reference group) received 10 mg/kg of furosemide, and the test groups (Groups III to VI) were administered 100 mg/kg and 200 mg/kg of methanol and water extracts of *O. bracteata* Wall., respectively. All the doses were prepared in the same volume of normal saline to ensure that each animal received the same amount of liquids. Immediately after administration, the animals were placed in metabolic cages (one animal per cage), specially designed to separate urine and feces. The urine, collected in graduated vials, was measured at the end of 6 h and expressed as mL/100 g of body weight per 6 hr.

Laxative Activity

The plant's laxative potential was measured using Mondal *et al.*[18] The same animals used in diuretic activity were used for laxative activity after a washing period of 3 weeks as the sacrifice of animals is not required to evaluate diuretic activity. Rats of either sex fasted for 12 hr before the experiment but with water provided *ad libitum*. The animals were divided into six groups of six each. The first group of animals serving as control were given vehicle (1% v/v Tween-80 in normal saline, 2 ml, p.o.), the second group received reference standard agar-agar (300 mg/kg, p.o.) in saline. Groups III to VI was administered methanol extracts and water extracts of *O. bracteata* Wall. at doses of 100 and 200 mg/kg, p.o. in a similar manner. Immediately after dosing, the animals were separately placed in cages suitable for collecting feces. After six hr of drug administration, the feces were collected and weighed. After that, food and water were given to all rats, and the fecal outputs were again measured after 24 hr.

The Diuretic and Laxative activity results were analyzed using one-way ANOVA test with the Dunnett hypothesis testing method.

RESULTS

Physicochemical Evaluation

The plant's physicochemical evaluations and successive extractive values are shown in Table 1. The plant material showed a higher amount of ash content as it is reported to contain a high amount of mineral elements such as Ca, Na, K, Mg, Fe, etc.[18] The plant material also showed a high swelling index, i.e., 11 mL/g of plant material, which shows the plant can be a rich source of mucilage. The water extract yield was the highest among all the extracts, followed by methanol extract.

HPTLC Profiling

Further, the UV spectrum of spots of *O. bracteata* Wall. Methanol extract with TLC system Ethyl Acetate: Acetic Acid: Formic Acid: Water (100:11:11:26) is shown in Figure 1. 5 spots at Rf (a) 0.976 (b) 0.580 (c) 0.559 (d) 0.494 and (e) 0.161 were scanned for UV spectrum. The above spots have λ_{max} at approx—330 nm, 365 nm, 370 nm, 375 nm, and 285 nm, respectively.

Elemental Analysis

The elemental analysis of plant material revealed the absence of various toxic heavy metals such as Arsenic, Lead, Cadmium, Chromium, etc. Other elements such as Copper, Cobalt, Aluminium, Manganese, and Nickle are also absent. The plant has the highest content of Potassium (672.12 ppm), followed by Calcium (118.83 ppm), Iron (10.52 ppm), Magnesium (6.46 ppm), and Zinc (1.16 ppm). The findings contrast

Table 1: Physicochemical Evaluation and Extraction of *O. bracteata* Wall.

Serial No.	Parameter	Value
1	Ash Content	
	Total Ash	25.26%
	Acid Insoluble Ash	3.61 %
	Water Soluble Ash	20.45 %
2.	Alcohol Extractable Matter	15.6 mg/g of plant material (1.56 %)
3.	Water content (Loss on Drying)	12.29 %
4.	Swelling Index	11 ml / g of plant material
5.	Foaming Index	<100
6	Successive Extraction Yield (%)	
	Pet Ether	0.81
	Chloroform	0.69
	Methanol	2.23
	Water	18.87

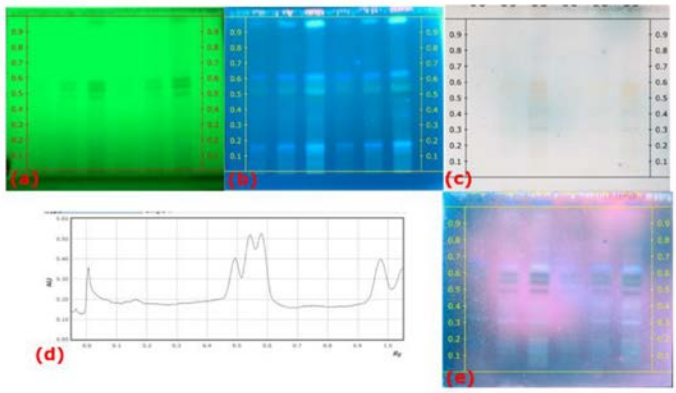

Figure 1: HPTLC Fingerprint of *O. bracteata* Wall. Methanol Extract (a) 254 nm (b) 366 nm (c) Anisaldehyde Sulphuric acid derivatized (d) densitometry at 254 nm (e) AS derivatized at 366 nm; TLC Mobile Phase System - Ethyl Acetate: Acetic Acid: Formic Acid: Water (100:11:11:26).

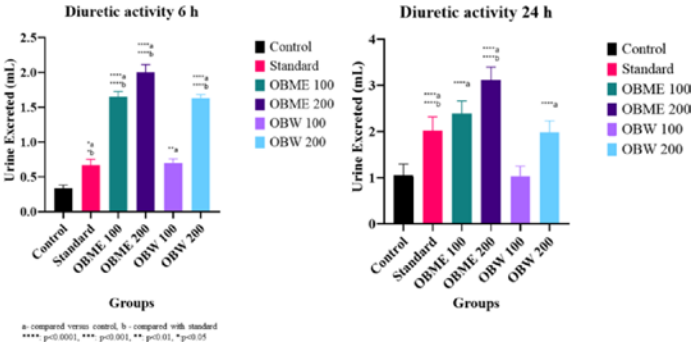

Figure 2: Diuretic Activity of *O. bracteata* Wall.; OBME: *O. bracteata* Wall. Methanol Extract; OBWE: *O. bracteata* Wall. Water Extract.

Table 2: Diuretic Activity of *O. bracteata* Wall.

Se. No.	Group Name	Diuretic Activity	
		Urine Collected (mL ± SD)	
		At 6 h	At 24 h
1	Normal Saline	0.33 ±0.12	1.05 ±0.22
2	Standard (Furosemide 10 mg/kg)	0..67 ±0.21	2.02 ±0.30
3	*O. bracteata* Wall. Methanol Extract (100 mg/kg)	1.65 ±0.19	2.83 ±0.28
4	*O. bracteata* Wall. Methanol Extract (200 mg/kg)	2.00 ±0.28	3.12± 0.28
5	*O. bracteata* Wall. Water Extract (100 mg/kg)	0.70±0.14	1.03±0.22
6	O. *bracteata* Wall. Water Extract (200 mg/kg)	1.63 ± 0.12	1.98±0.25

the presence of heavy metals in the same plant occurring in Pakistan.[19] Additionally, the presence of Zinc and Magnesium are in accordance with the leaves found in Punjab province of Pakistan.[20] The high ash content of the plant can be attributed to the salts of Potassium and Calcium.

Diuretic Activity

The diuretic activity of the plant extracts are summarized in Figure 2 and Table 2. The methanol extract at doses 100 mg/kg (1.65 mL ± 0.19) and 200 mg/kg (2.00 mL ± 0.28) and aqueous extract at dose 200 mg/kg (1.63 ± 0.12) showed highly significant diuretic activity (p<0.0001) at 6 h compared to standard furosemide (0.67 mL ± 0.21). Whereas, methanol extract at doses 200 mg/kg (3.12 mL ± 0.28) showed highly significant diuretic activity (p<0.0001) at 24 hr compared to standard furosemide (2.02 mL ± 0.30).

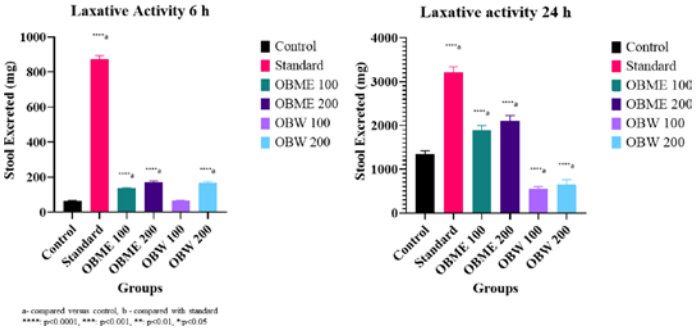

Figure 3: Laxative Activity of *O. bracteata* Wall. OBME: *O. bracteata* Wall. Methanol Extract; OBWE: *O. bracteata* Wall. Water Extract.

Table 3: Laxative Activity of *O. bracteata* Wall.

Se. No.	Group Name	Stool Excreted (mg ± SD)	
		At 6 h	At 24 h
1	Normal Saline	64.83 ± 6.43	1346.00 ±74.46
2	Standard (Agar-Agar)	872.50 ±52.41	3210.67 ±124.07
3	*O. bracteata* Wall. Methanol Extract (100 mg/kg)	135.67 ±11.48	1889.50 ±108.87
4	*O. bracteata* Wall. Methanol Extract (200 mg/kg)	171.50±17.42	2106.00± 120.59
5	*O. bracteata* Wall. Water Extract (100 mg/kg)	65.67±5.28	554.67±51.24
6	O. *bracteata* Wall. Water Extract (200 mg/kg)	169.33 ± 13.37	648.83±112.54

Laxative Activity

The laxative activity of the plant extracts is summarized in Figure 3 and Table 3. The methanol extract at doses 100 mg/kg (135.67 mg ± 52.41) and 200 mg/kg (171.50 mL ± 17.42) and aqueous extract at dose 200 mg/kg (169.33 mg ± 13.37) showed highly significant laxative activity (p<0.0001) at 6 h compared to normal saline group (64.83 mg ± 6.43). Whereas the amount of stool excreted in aqueous extract groups of 100 mg/kg (554.67 mg ±51.24) and 200 mg/kg (648.83 mg ±112.54) was significantly lower compared to the normal saline group (1346.00 ±74.46). However, all the extracts showed significantly lesser laxative activity (p<0.0001) than the standard agar-agar group at 6 and 24 hr. Thus, methanol extract of the plant showed mild laxative activity, whereas aqueous extract showed mild antidiarrheal activity.

DISCUSSION

Preliminary phytochemical investigation and TLC profiles revealed the presence of flavonoids/hydroquinone/phenolics in methanol extract, according to reported phytochemical investigations.[16] The benzoquinones, coumarins, caffeic acid derivatives, p-hydroxybenzoic acid analogs, rosamarinic acid, eritrichin, salvianolic acid, and analogs, lignans, and glycosides in the plant have been reported.[13,15] Rosamarinic acid and caffeic acid, constituents of the plant, induce diuretic, natriuretic, and Ca^{2+} sparing effects in rats.[21] Several human carbonic anhydrase

(CA) isoforms are expressed in the functional unit of the kidney, i.e., nephron, and play a key role in inhibiting urinary excretion. Several CA inhibitors, such as Acetazolamide and structurally related sulfonamides, act as diuretics and are used to treat edema due to congestive heart failure and drug-induced edema.[22] p-hydroxybenzoic acid and caffeic acid, constituents of the plant, inhibit all isozymes of human and mammalian carbonic anhydrase.[23-24] Rosmarinic acid and eritrichin containing *Eritrichium sericeum* Lehm. preparation demonstrated increased renal excretory function.[25] Salvianolic acid and its analogs are reportedly possessing carbonic anhydrase inhibitory activity.[26] At the same time, coumarins have a similar action on carbonic anhydrase enzyme.[27] Additionally, elemental analysis of plant material detected Potassium at a level of 672.12 ppm. Thus, the diuretic potential of the methanolic extract can be attributed majorly to carbonic anhydrase inhibitory activity of constituent compounds, in addition to natriuretic, Ca^{2+} sparing activity, and increased renal excretory function. The milder diuretic action of the aqueous extract can be due to the presence of K, Ca, and Na salts in aqueous extracts.[28] Thus, the traditional use of *Gojihva* as *mutral* (diuretic) is confirmed with a phytochemical basis. However, detailed studies of the extracts and constituents are required to establish the mechanism of action.

Further, the antidiarrheal activity of the plant has been reported in study.[29] The significantly less amount of stool excreted by water extracts groups at 24 hr compared to the normal saline group is in accordance with the same. In contrast, the methanol extract of the plant showed milder laxative activity compared to the normal saline group. Furhter, pharmacological studies and phytochemical investigation are required to determine bioactive constituents and mechanisms of action.

CONCLUSION

Thus, the traditional use of *O. bracteata* Wall. as a diuretic is established, with probable attribution to carbonic anhydrase inhibitory activity of constituent compounds. Methanol extract's further pharmacological and phytochemical investigations may reveal novel compounds with diuretic potential.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Ethics Approval and Consent to Participate

The protocol for diuretic and laxative activity was approved by Institutional Animal Ethics Committee, School of Pharmacy, R K University vide proposal no. RKCP/COI/RA/21/107.

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