Research Article

Toxicity Study of *Datura stramonium* L. and *Hyoscyamus niger* L. in Reference to Unani Concept of Therapeutic Interchange

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Received: 21-09-2022; **Revised:** 26-11-2022; **Accepted:** 04-12-2022; **Published on:** 15-12-2022.

ABSTRACT

Aims: Traditional systems of medicine are often blamed for the use of toxic drugs. On the basis of centuries-old evidence of their safety, these systems actually use a number of drugs that are alleged to be harmful. However, these healthcare systems have devised methods for eliminating hazardous components from such medications before consumption. *Datura stramonium* L. and *Hyoscyamus niger* L. are commonly used in Unani Medicine with minimum or no side effects, but without sufficient safety data. The present study includes safety studies of the two drugs as a comparative study because the two drugs are used interchangeably.

Methodology: The present study was carried according to the guidelines of Organization for Economic Cooperation and Development (OECD) test no. 423: acute oral toxicity - acute toxic class method. A single oral dose of 2000 mg/kg and 5000 mg/kg of each of the hydroalcoholic and aqueous extracts of the seeds of the drugs *D. stramonium* and *H. niger* was given to each group. Animals (female Wistar rats) were observed individually for fourteen days for their general appearance, behavioral responses, and for any signs of toxicity and mortality.

Result: The study revealed no mortality; however, sedation and loss of activities were found in both drugs. Pronounced effect was seen in hydroalcoholic extract *D. stramonium* (5000 mg/kg) treated animals as compared to *H. niger.*

Conclusion: These two drugs may be used safely in therapeutic doses mentioned in Unani literature.

Keywords: *Datura stramonium, Hyoscyamus niger*, OECD, Therapeutic interchange, Toxicity study.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v77i02.027

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v77i02.027

INTRODUCTION

Jimson weed or Devil's snare are two frequent names for the narcotic *D. stramonium.* India is home to about ten species. An annual herb that grows between 0.6 and 1.2 meters tall and is found all over India.[1] The matured seeds of *D. stramonium* have the highest concentration of the plant's active constituents, despite the fact that all parts of it are toxic. Alkaloids found in it are poisonous to humans and can cause hallucinations and even death.[2] It contains 64 tropane alkaloids, with hyoscyamine, hyoscine and atropine being the main ones. Minor alkaloids commonly include aposcopolamine, tigloidin, apoatropin, 7-hydroxyhyoscyamine, hyoscyamine N-oxide, ditigloyloxytropane and scopolamine N-oxide.[3] The plant has the ability to reduce inflammation, stimulates Central Nervous System (CNS), and actively clears respiratory tract, which benefits the respiratory system and maintains the health of the teeth and skin.[4] It is abundant in substances that have anticholinergic potential and can be used to treat organophosphate toxicity symptoms.[2] Among the pharmacological effects are analgesic, anesthetic, antiasthmatic, anticholinergic, anticholinesterase, antihistaminic, anti-inflammatory, antiparkinsonian, antiseptic, antisialagogue, antispasmodic, aphrodisiac, bronchoconstrictor, sedative, CNS-stimulant, fungicide, intoxicant, lactifuge, mydriatic, narcotic, nervine, parasympatholytic and has poisonous effect.[5]

Its widespread distribution and high toxicity may be closely linked to its frequent poisoning (deliberate or unintentional). Regardless of the portion consumed, *D. stramonium* may result in consequences that are challenging to diagnose. Due to the fact that it has been linked to numerous suicide and homicide cases in India and other parts of the world, strict laws outlawing its cultivation have been put into place in several locations.[6-9]

Certain drugs are used as therapeutic interchange for one another.[10-12] According to Unani Medicine, *D. stramonium* is therapeutic interchange of *H. niger* for many pharmacological actions, especially sedative (*Musakkin-i-Dimagh*), anaesthetic (*Mukhaddir*), hypnotic (*Munawwim*) and astringent (*Qabid*), styptic (*Habis-i-Dam*), retentive (*Mumsik-i-Mani*), antispasmodic (*Dafi'-i-Tashannuj*), analgesic (*Musakkin-i-Alam*).[10-12] Therefore, the two drugs have been comparatively studied for their toxicity.

Henbane, or *Hyoscyamus niger* L., belongs to Solanaceae family. It has three varieties viz. White, red and black. It is a biannual herb with a height of 80 cm that thrives in rocky, arid areas and adjacent to roads.[1] The flowers colors vary from yellow to dull green, and its leaves are shaped like a heart. The seeds are dark grey, somewhat larger than a mm, irregularly reniform or subquadrate and are used medicinally. The main alkaloids found in the various portions are atropine, hyoscyamine and hyoscyine.[13-15]

Additionally, traces of apohyoscine, daturamine, apoatropine, hyoscyamine-N-oxide are present. The relatively higher concentration of hyoscine, which has a central narcotic effect, modifies the activity of *H. niger*.[3,15] It has mydriatic, narcotic and anodyne effects. [15] It is primarily used as a sedative in nervous disorders and breathing problems like whooping cough and is used in place of opium when the latter is prohibited. Additionally, it reduces urinary tract spasms and works as a counterbalance to purgatives gripping effects. External use of *H. niger* leaves for pain relief has been reported.[16]

Clinical signs and symptoms of both medications are extremely diverse. They include tachycardia, mydriasis, decreased bowel movements, dry skin and mouth, arrhythmia, nausea, convulsion, agitation, slurred speech, confusion, thirst, dysphagia, blurred vision, pyrexia, headache, urinary retention, photophobia, hyperreflexia, hallucinations, warm flushed skin, drowsiness, delirium, confusion, aggressive behavior, coma and disorientation. [17,18]

Despite its widely reported toxicity and use in Unani Medicine as a component of some compound medications, there is little research on its toxicity. To assess the toxicity of these medications, some animal experiments were conducted. T. Ogunmoyole *et al.* research indicates that *D. stramonium* is poisonous and can harm the liver, heart, kidneys and brain, among other organs. The extraction solvent affects the degree to which it is hazardous to the various organs.[2] In another study, male Albino-Wistar rats were used to analyse the results of scopolamine and atropine administration in acute, subacute and chronic toxicity study. The haematological study showed a considerable reduction in RBC, HCT, HBG and WBC, as well as numerous Centro lobular necrotic regions, dilated central veins, congestion in blood in the groups treated with drug.[19] Z. Benouadah *et al.* conducted one study on the seeds of *D. stramonium*. This study aimed to assess the alkaloids isolated from *D. stramonium* seeds. Haematological studies revealed that alkaloids at 60 mg/kg doses significantly decreased haemoglobin, haematocrit and RBC levels. The plasma levels of AST, urea, ALT, K+, creatinine and LDH, were significantly changed after alkaloids were administered. After the subacute (28 days) study, with dose of 16 mg/kg, AST, GGT, ALT, Na+, PLA and K+ concentrations markedly increased. All four blood component levels declined, *viz*., RBC, haemoglobin, haematocrit, and platelet. The heartbeat and breathing cycle rates in the treated mice also increased, against the controls. During the histological analysis, the kidney and, to a lesser extent, the liver displayed high vacuolization and inflammation levels.[20]

Although *H. niger* is less poisonous than *D. stramonium*, both have potential side effects. On the acute and subacute toxicity of *H. niger*, insufficiently reliable animal data is known. One study showed that when mice were given the water extract of *H. niger* seed to conduct the acute toxicity assay, none of the animals perished from intoxication.[16] Accidental ingesting of some *H. niger* seeds has led to toxic symptoms that can occur one to four hours after ingesting the seed and last up to 48 hours.[21]

MATERIALS AND METHODS

Drugs and Chemicals:

The medicines were purchased from a local Bengaluru market. All drugs were identified by Dr. S. Noorunnisa Begum (Senior Assistant Professor, FRLHT, Bangalore). Solvents of an analytical grade were used in this study.

Powdering of Drugs*:* The seeds of *D. Stramonium* and *H. niger* were finely powdered in a mixer grinder separately. These powders were stored separately in air-tight glass jars, which were used for further purposes.

Extraction: Aqueous and hydroalcoholic extracts were obtained using the Soxhlet apparatus.

Animals

During the experiment, young, healthy, nulliparous, and non-pregnant, weighing 150-200 grams ± 20 grams **Female Wistar Rats** were used.

Housing of Animals: Study was started, after receiving ethical approval from the Institutional Animal Ethics Committee (IAEC) of the National Institute of Unani Medicine (NIUM), Bangalore, vide number (IAEC /06/16/IA/01). Animals were obtained from Biogen, a licensed breeder. The animals were permitted a week of acclimatization preceding experiment. The experimental protocol and methods for caring for the animals adhered to CPCSEA regulations. Throughout the experiment, they were kept in standard lab settings, fed a standard diet and allowed to drink water ad libitum. They were maintained at room temperature (18 to 29 ° C) in hygienic polypropylene cages and average humidity at (30-70%) with standard laboratory conditions.

Acute Toxicity Study: Acute Toxicity was conducted in accordance with OECD Guidelines (423) .[22] One of four predetermined levels was chosen as the dose range for the initial dose, i.e., 2000 mg/kg. With free access to water, the female Wistar rats were fasted for the entire night. The test medicine was given orally in a single dose and the effects were monitored immediately, at least once within the first 30 minutes and occasionally throughout the first 24 hours. A special focus was placed on monitoring general behavior, changes in body weight, average food intake, potentially hazardous symptoms and death within the first four hours and then every day for 14 days. At a dose of

2000 mg/kg body weight, no adverse effects of the test drug were seen. The next dose 5000 mg/kg, was further evaluated. Histopathology and Biochemistry were not carried out.

Experimental design:

- Control group -10 ml/kg of Carboxymethyl cellulose solution (CMC) solution
- Test group A: Aqueous extract of *D. stramonium* (2000 mg/kg)
- Test group B: Aqueous extract of *H. niger* (2000 mg/kg)
- Test group C: Hydroalcoholic extract of *D. stramonium* (2000 mg/kg)
- Test group D: Hydroalcoholic extract of *Hyoscyamus niger* (2000 mg/kg)
- Test group E: Aqueous extract of *D. stramonium* (5000 mg/kg)
- Test group F: Aqueous extract of *H. niger* (5000 mg/kg)
- Test group G- Hydroalcoholic extract of *D. stramonium* (5000 mg/kg)
- Test group H: Hydroalcoholic extract of *H. niger* (5000 mg/kg)

Rats were randomized into eight groups: Plain control and test groups (A, B, C, D, E, F, G and H). The number of female animals in each group was three, according to doses, i.e., 2000 mg/kg & 5000 mg/kg and then repeated for the same dose. One animal was kept in the control group along with every group and received a vehicle, i.e., 10 ml/kg of 0.5% Carboxymethycellulose (CMC) solution. Other test groups (Groups A -H) were administered with test drugs, respectively. General Behavior Pattern was observed by exposing each animal to an open area. Animals were observed and recorded systematically 1hr., 2hr., 3hr., 4hr., 5hr., 6hr., 12hr. and for 24 hours daily for fourteen days. Changes in the skin, hair, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous systems were among the visible observations. After 14 days of observation, rats were sacrificed.

RESULTS

Aqueous and Hydroalcoholic Extract of *D. stramonium* (2000 mg /kg)

The administration of the hydroalcoholic and aqueous extract of D. stramonium did not significantly alter the rats' general behaviour and physiological activities. The rats' heart rate and respiratory activity were noticeably elevated during the first half hour, followed by hypoactivity for three hours and then diminished activity for 24 hours. The animals lost their capacity to climb and move, they were unable to walk without assistance, confusion was visible, their pupils dilated for 24 hours, and they were lethargic for at least one day. The hydroalcoholic group had all of these indications and symptoms for almost 24 hours longer than the aqueous group, after which they resumed their regular activities. Administration of both extracts did not show any decreased food intake; however, water intake was significantly increased, more in the hydroalcoholic group than aqueous groups. There was no significant alteration in body weight (1-14 days), animals showed no toxicity, and no death was reported (Table 1).

Aqueous and Hydroalcoholic Extract of *H. niger* (2000 mg/kg)

The administration of both *H. niger* extracts did not cause noticeable variations in the physiological or general behaviour of rats. However, there was little movement in the first half hour, increased heart rate and respiratory activity, hypoactivity for three hours and diminished activity for some hours. The rats were also unable to walk freely, showed signs of confusion, had dilated pupils for 12 hours and had weak grip strength. The hydroalcoholic group experienced these signs and symptoms for approximately 12–14 hours longer than the aqueous group, after which they resumed everyday activities. Food intake was not observed to be reduced after administration of either extract. However, water intake was considerably increased in the hydroalcoholic group than in the aqueous groups. Animals did not exhibit any symptoms of toxicity, there was no substantial change in body weight (1–14 days) and no deaths were noted. The activities in this group were less reduced than in the *D. stramonium* test groups (Table 2).

Aqueous and Hydroalcoholic Extract of *D. stramonium* (5000 mg/kg)

Administration of an aqueous and hydroalcoholic extract made from *D. stramonium* seeds resulted in severe clinical signs, such as tachycardia and accelerated breathing. In addition, rats' locomotor activity increased for the first half hour, then animals' activities were diminished and sedative effects were visible for over three hours. The clinical presentation of female rats given these extracts was marked by a relatively rapid onset of symptoms, such as tachycardia, as a result of their impact on the parasympathetic nervous system by restricting vagal stimulation, and severe agitation as a result of their reaching the central nervous system., followed by sedative action for three hours and then diminished activity for 48 hours in the aqueous groups and not able to move for 72 hours in the hydroalcoholic group. In the hydroalcoholic and aqueous groups, pupils were dilated for 48 and 72 hours, respectively, grip strength was lost, the animals lost their ability to climb and move, and they became confused and lethargic for at least a day. All these symptoms were present in the hydroalcoholic group for nearly 48 hours, longer than in the aqueous group, before returning to normal. Administration of both extracts did not show any decreased food intake. However, water intake was significantly increased in hydroalcoholic groups than in aqueous groups, especially in the first 24 hours. There was no significant alteration in body weight (1-14 days) and animals also did not show any signs of toxicity (Table 3).

Table 1: Effect of aqueous and hydroalcoholic extract of *Datura stramonium* L. according to dose (2000 mg/kg) in acute toxicity study

S. No.	Response	Control group CMC solution (10 ml/kg)	Aqueous extract of *Datura stramonium* L. (2000 mg/kg)	Hydroalcoholic extract of *Datura stramonium* L. (2000 mg/kg)
1	Alertness	Average	Average	Average
2	Grooming	Average	Average	Average
3	Restlessness	Absent	Absent	Absent
4	Touch response	Average	Reduced	Reduced
5	Pain response	Normal	Reduced	Reduced
6	Convulsion	Absent	Absent	Absent
7	Tremors	Absent	Absent	Absent
8	Sedation	Normal	Present	Present
9	Righting reflex	Normal	Reduced	Reduced
10	Grip strength	Normal	Reduced	Reduced
11	Pinna reflex	Normal	Reduced	Reduced
12	Corneal reflex	Normal	Reduced	Reduced
13	Pupils	Normal	Dilated	Dilated
14	Urination	Normal	Normal	Normal
15	Salivation	Normal	reduced	Reduced
16	Skin color	Normal	Normal	Normal
17	Lacrimation	Normal	Normal	Normal
18	Food intake	Average	Average	Average
19	Water intake	Normal	Increased	Increased
20	Mortality	None	None	None

Table 2: Effect of aqueous and hydroalcoholic extract of *Hyoscyamus niger* L. according to dose (2000 mg/kg) in acute toxicity study

S. No.	Response	Control group CMC solution (10 ml/kg)	Aqueous extract of *Hyoscyamus niger* L. (2000 mg/kg)	Hydroalcoholic extract of *Hyoscyamus niger* L. (2000 mg/kg)
1	Alertness	Average	Average	Average
2	Grooming	Average	Average	Average
3	Restlessness	Absent	Absent	Absent
4	Touch response	Average	Reduced	Reduced
5	Pain response	Normal	Reduced	Reduced
6	Convulsion	Absent	Absent	Absent
7	Tremors	Absent	Absent	Absent
8	Sedation	Normal	Present	Present
9	Righting reflex	Normal	Reduced	Reduced
10	Grip strength	Normal	Reduced	Reduced
11	Pinna reflex	Normal	Reduced	Reduced
12	Corneal reflex	Normal	Reduced	Reduced
13	Pupils	Normal	Dilated	Dilated
14	Urination	Normal	Normal	Normal
15	Salivation	Normal	Reduced	Reduced
16	Skin color	Normal	Normal	Normal
17	Lacrimation	Normal	Normal	Normal
18	Food intake	Average	Average	Average
19	Water intake	Normal	Increased	Increased
20	Mortality	None	None	None

Table 3: Effect of aqueous and hydroalcoholic extract of *Datura stramonium* L. according to dose (5000 mg/kg) in acute toxicity study

S. No.	Response	Control group CMC solution (10 ml/kg)	Aqueous extract of *Datura stramonium* L. (5000 mg/kg)	Hydroalcoholic extract of *Datura stramonium* L. (5000 mg/kg)
1	Alertness	Average	Absent	Absent
2	Grooming	Average	Average	Average
3	Restlessness	Absent	Absent	Absent
4	Touch response	Average	Reduced	Reduced
5	Pain response	Normal	Reduced	Reduced
6	Convulsion	Absent	Absent	Absent
7	Tremors	Absent	Absent	Absent
8	Sedation	Normal	Increased	Increased
9	Righting reflex	Normal	Reduced	Reduced
10	Grip strength	Normal	Reduced	Reduced
11	Pinna reflex	Normal	Reduced	Reduced
12	Corneal reflex	Normal	Reduced	Reduced
13	Pupils	Normal	Dilated	Dilated
14	Urination	Normal	Normal	Normal
15	Salivation	Normal	Reduced	Reduced
16	Skin color	Normal	Normal	Normal
17	Lacrimation	Normal	Normal	Normal
18	Food intake	Average	Average	Average
19	Water intake	Normal	Increased	Increased
20	Mortality	None	None	None

Table 4: Effect of aqueous and hydroalcoholic extract of *Hyoscyamus niger* L. according to dose (5000 mg/kg) in acute toxicity study

S. No.	Response	Control group CMC solution (10 ml/kg)	Aqueous extract of *Hyoscyamus niger* L. (5000 mg/kg)	Hydroalcoholic extract of *Hyoscyamus niger* L. (5000 mg/kg)
1	Alertness	Average	Absent	Absent
2	Grooming	Average	Average	Average
3	Restlessness	Absent	Absent	Absent
4	Touch response	Average	Reduced	Reduced
5	Pain response	Normal	Reduced	Reduced
6	Convulsion	Absent	Absent	Absent
7	Tremors	Absent	Absent	Absent
8	Sedation	Normal	Increased	Increased
9	Righting reflex	Normal	Reduced	Reduced
10	Grip strength	Normal	Reduced	Reduced
11	Pinna reflex	Normal	Reduced	Reduced
12	Corneal reflex	Normal	Reduced	Reduced
13	Pupils	Normal	Dilated	Dilated
14	Urination	Normal	Normal	Normal
15	Salivation	Normal	Reduced	Reduced
16	Skin color	Normal	Normal	Normal
17	Lacrimation	Normal	Normal	Normal
18	Food intake	Average	Average	Average
19	Water intake	Normal	Increased	Increased
20	Mortality	None	None	None

Aqueous and Hydroalcoholic extract of *H. niger* (5000 mg /kg)

An individual dose of both aqueous and hydroalcoholic extracts was administered and on the first day, this dose raised the cardiac and respiratory rates compared to control values. Significant changes were observed in physiological measures such as heart and respiration rates and body temperature. After 30 minutes of substantial activity, there was reduction in the rats' locomotor activity, followed by a 2-hour sedative phase. Then there was a decline in activity for 20–24 hours in the hydroalcoholic and aqueous groups. Animals lost their grip strength, were unable to climb or move for at least a day, were confused, had dilated pupils for 20–24 hours in the case of the hydroalcoholic group and were lethargic for at least a day. Before returning to normal, these symptoms were present in the hydroalcoholic group for about 24 hours longer than in the aqueous group. There were no notable differences in the amount of food consumed versus the control group. However, it was found that the hydroalcoholic group consumed much more water than the aqueous group, especially in the first 24 hours. In terms of body weight, there were often no appreciable variations between the treatment and control groups. Additionally, there were no toxicology-related behaviours or animal deaths noted (Table 4).

DISCUSSION

There is a lot of research interest in medication poisoning. *D. stramonium* toxicity has been the subject of numerous reports, indicating that the likelihood of such an incidence is not very rare. [23] Younger people who use the plant recreationally know that it induces the desired intoxication but are unaware of the health concerns linked to this usage. [7] This is crucial for children who are particularly sensitive than other age groups because they cannot comprehend the danger of being poisoned when mistakenly consume pieces of the plant as a food ingredient. [9] The affected individuals' varied appearances and changing mental status contribute to the challenges in making an accurate diagnosis. Jimsonweed poisoning can happen to people of all ages, which healthcare professionals and public health officials should be aware of. [24,25]The presence of tropane alkaloids, comprising the anticholinergic drugs scopolamine and atropine, as well as a methylated nitrogen atom (N-CH3), is assumed to be the cause of the neurotoxicity of both drugs.[26]This herb has been used to treat several ailments in Unani medicine and is an important ingredient of many compound drugs, therefore, it is crucial to comprehend its therapeutic dose. Adult human dose of *D. stramonium* mentioned in classical Unani literature is 500 mg while that of *H. niger* is 500-1250 mg and even the temperament of *D. stramonium* is colder and drier in fourth degree while that of *H. niger* is less cold and dry in third degree.[11,12]This proves that Unani doctors also took drug dosage into account while recommending alternatives. The primary chemicals constituents involved in the action of *D. stramonium* and *H. niger* are atropine, scopolamine and hyoscyamine. *D. stramonium* has a higher atropine content than *H. niger*.[10] This co relates with the dose as well as temperament, mentioned in Unani medicine and further justifies dose, temperament and phytoconstituents to be taken together to contrivance therapeutic interchange drug. It is evident that *H. niger* is a safer therapeutic interchange to *D. stramonium*.

This study also demonstrated that *D. stramonium* and *H. niger* are safely tolerated till the dose of 5000 mg/kg. However, they produce a sedative, hypnotic and mydriatic effect for up to 24-72 hours. Nevertheless, these effects are more prominent in *D. stramonium* than in *H. niger*.

CONCLUSION

This study proves the anticholinergic potential of *D. stramonium* and *H. niger,* due to phytoconstituents such as atropine, scopolamine and hyoscyamine. *H. niger* being less toxic than *D. stramonium* makes it a safer alternative to use in desired medications. *D. stramonium* displayed an increased response to the same dose as compared to *H. niger*; it was determined that the toxicity was a drug and dose-dependent phenomena. The animal behaviors during the observation period of fourteen days point to the safety of a single dosage of both aqueous and hydroalcoholic extracts, even at doses as high as 5000 mg/kg of animal body weight. To confirm the safe use of these drugs, more research, including subacute, special and chronic toxicity assessments, are required. These studies are critical to better understand and verify the safety profile of these therapeutic interventions.

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Source of Support: The authors received financial support from NIUM (M/o of AYUSH, Govt. of India), Bengaluru for research, but no support for publication from any source.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.