ADVERSE REACTIONS OF SOLENOSTEMMA ARGELE LEAVES, EXTRACTS AND ALKALOIDS TABLETS ADMINISTERED TO PATIENTS
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ABSTRACT

These trials were performed for the evaluation of the safety and effectiveness of Solenostemma argel tablets. In this study we started with a low dosage, and gradually increasing the dose cautiously, and watching carefully for toxic effects. One hundred healthy male subjects participated in these clinical trials. These trials were conducted under the supervision of a clinicians, and started with low doses, e.g. one tablet of one of S. argel products, three times daily, and gradually increased till the highest dose was attained, which was four tablets three times a day, for each of the leaves, extracts or alkaloids tablets and the occurring adverse reactions were reported.

INTRODUCTION

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. It was an integral part of the development of modern civilization. Primitive man observed and appreciated the great diversity of plants available to him. The plants provided food, clothing, shelter, and medicine. Much of the medicinal use of plants seems to have been developed through observations of wild animals, and by trial and error. The World Health Organization (WHO) estimates that four billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all indigenous peoples’ traditional medicine and a common element in Ayurvedic, homeopathic, naturopathic, traditional oriental and Native medicine. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value. There are already 100 well-known, biologically-active compounds from 1000 of the tropical species that are used in folk medicine. Solenostemma argel (Del) Hayne is known locally in Sudan as ‘hargal’, and belongs to the family Asclepiadaceae. Other members of the family include S. oleifolium (Nectoux) Bullockt Bruce, and S. triste (Nees) K. Muell. It is an erect shrub reaching a height of 60-100cm, with many velvety, pubescent branches from the base. It is distributed in Saudi Arabia, Egypt, Libya, Chad and Palestine. In Sudan, it is indigenous in the northern regions between Barbar and Abu Hamad. S. argel leaves were, at one time, used to adulterate Khartoum Senna. Some Uses of Solenostemma argel in Folkloric Medicine.

In treatment of GIT disturbances, hypercholesterolemia and diabetes mellitus; and externally, in poultice form, as anti-inflammatory and anti-rheumatic, and Inhalation of its smoke in the treatment of measles and cold. The stem is generally used as antispasmodic and to treat cough. ‘Hargal’ infusion is used to treat diabetes and jaundice; it is also used to treat measles.
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Hayne has been considered as an effective remedy for cough. Infusion of the leaves is usually indicated for gastrointestinal cramps, cold and urinary tract infections. It is also used as a stomachic, anti-colic, and anti-syphilitic when used for prolonged period of 40 to 80 days\(^5\). The solenostemma argel contain flavonoids, kaempferol, quercetin, rutin, flavonols, flavanones, chalcones and alkaloids in \textit{S. argel}. Also they contain pregnancy ester glycosides in \textit{S. argel} extracts. Phytochemical studies of the leaves, stems and flowers revealed the presence of \(\alpha\)-amyrin and \(\beta\)-amyrin, \(\beta\)-sitosterol, 7-methoxy-3\(\alpha\)-22\(\alpha\)-dihydroxy-stigmasterone, ethoxy derivative of vangurolic acid, an unidentified sterol. Moreover, they detected the presence of flavonoids and saponins in the different organs, and alkaloids and/or nitrogenous bases in the leaves, stems and flowers\(^\text{8,9} \text{ S. argel} \). 

\textit{Solenostemma argel} contains an acid resin, glycoside, choline, phytosterols and amyrins. It is used in indigenous medicine as an effective remedy for coughs. The infusion of its leaves is used for gastro-intestinal cramps and infections of the urinary tract\(^6\).

Broadly speaking any adverse drug effect may be thought of as a manifestation of drug toxicity. It will be useful, however to consider separately and in considerable detail, the following specific categories of adverse drug effects: idiosyncrasy, drug allergy, tolerance and physical dependence, mutagenesis, teratogenesis and carcinogenesis. It is important to consider the adverse effects that are dose related, and experienced by most or all of the exposed population, usually at drug levels (or doses) in excess of those associated with a therapeutic action. Sometimes a toxic effect is simply an extension of the therapeutic effect at a higher dose level; often on the other hand, toxicity takes the form of a side effect more or less unrelated to the primary drug action. Examples are dryness of mouth seen frequently with atropine or hyoscine, and tachycardia and breathlessness with \textit{S. argel} toxic doses. These trials were performed for the evaluation of the safety and effectiveness of \textit{Solenostemma argel} tablets and the assurance of safety and protection of the human subjects participating in these investigations.\(^10\) This was done because this drug, if proven safe and effective, should be adopted for clinical use and would be a fairly straightforward task. The trial would be started with a low dosage, and gradually increasing the dosage cautiously, and watching carefully for toxic effects. If the deduced therapeutic effect could be obtained with little toxicity in a large number of patients, it would be acceptable to increase the dosage well beyond the therapeutically effective range, with the aim of assessing by how much the therapeutic dose could be exceeded before toxicity ensued.

**MATERIALS AND METHODS**

**Plant material:**

\textit{Solenostemma argel} leaves from local sudanese market.

**Tablet formulation:**

The phytochemical methods adopted in the course of this work included preparation of powdered \textit{Solenostemma argel} leaves, after inspection and identification, reduction to the required particle size, followed by sieving for powder separation and analysis. These \textit{Solenostemma argel} leaves powders were used for determination of identity, purity and quality of \textit{S. argel}; for direct incorporation into tablet formulations, or for preparation of different extracts incorporated into tablet formulations. These included preparation and concentration of water extracts of \textit{S. argel} leaves, preparation of total alkaloids of \textit{S. argel} leaves.\(^10\)

**Questionnaire:**

This questionnaire was distributed among individuals who had the practice of using herbal medicines.

**Monitoring Possible Adverse Reactions in Healthy Volunteers Receiving \textit{Solenostemma argel} Leaves, extract and alkaloids Tablets:**

Ten healthy male subjects, from the staff and students of the Faculty of Pharmacy, University of Khartoum, participated in these clinical trials at their own choice and will. They either use \textit{Solenostemma argel} leaves in their ordinary life as a decoction or with milk, as a beverage and flavour, or as a medicine for treatment of various gastrointestinal disturbances or minor ailments. These subjects were well informed about the purpose and nature of the investigation, the preparations they were going to administer, the potential risk involved, and the possible side effects or adverse reactions which were likely to occur. Following this information delivered to them, each of these volunteers signed a written consent indicating his participation in this study at his own will and choice. Each of these healthy subjects was subjected to a medical examination by a clinician; blood pressure and heart beats were measured before and after treatment, and all of them proved to be in very good health. Then, to monitor any possible side effects or adverse reactions to \textit{S. argel} preparations, these trials were conducted under the supervision of a clinician, and started with low doses, e.g. one tablet of one of \textit{S. argel} products, three times daily, and gradually increased till the highest dose used was attained, which was four tablets three times a day, for each of the leaves tablets.\(^10\)

**Therapeutic Effectiveness of \textit{Solenostemma argel} Leaves, Extracts and Alkaloids Tablets Administered to Patients:**

These clinical trials were organized in three teaching hospitals, namely Khartoum teaching hospital, Khartoum North teaching hospital and University of Khartoum clinic, under the supervision four physicians. One hundred patients, selected randomly, were 20-70 years old, and 40 males and 60 females. They were complaining of gastrointestinal disturbances, and diagnosed as having gastritis, indigestion, heartburn, flatulence, irritable bowel syndrome, renal colics, or colics due to menstrual pain.\(^10\)
RESULTS AND DISCUSSION:

Questionnaire results:

The following findings were recorded:

Concerning the effectiveness of the medicinal herb used, 60% of the participants felt completely relieved of pain after a single administration of the herbal medicine; 26% percent used the drug several times due to repeated attacks of pain; four percent had mild pain relief; and 15% percent did not feel relieved of their colics and pains. With regard to the origin of instructions to use a herbal medicine, 70% were advised by their parents and relatives, 21% percent by a pharmacists, and only four percent by doctors. With respect to the herbal medicine source or supply, 62% percent obtained it from the Sudanese herbal medicines local market and 38% from abroad. When considering the part of the medicinal plant used, 30% of used the whole plant, twenty two percent the roots, fifteen percent the leaves, ten percent the stems, 9% percent the seeds, 6% the fruits, 2% percent the flowers, and 6% percent used other parts of the plants or plant products. With regard to the quantity or dose of herbal medicine to be used, 85% used the preparation just by guessing or used an arbitrary quantity, while 15% either measured or weighed specified amount of the herbal medicine. Concerning the medicinal herb preparation, 75% prepared the preparation by themselves or by their relatives at home, while 25% percent of these preparations were dispensed by an herbal doctor. When considering the types of herbal preparations used, 45% percent were decoctions, 38% percent were powder type, 17% were macerated plants preparations.

Monitoring Possible Adverse Reactions in Healthy Volunteers Receiving Solenostemma argel Leaves, Extracts and Alkaloids Tablets

Table 1: Adverse Reactions Recorded in Healthy Volunteers Receiving Solenostemma argel Leaves, Extracts and Alkaloids Tablets*  

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Age (year)</th>
<th>Heart Beats</th>
<th>Blurred Vision</th>
<th>Nausea and/or Vomiting</th>
<th>Mouth Dryness</th>
<th>Stomach Upset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*: Two Tablets of Each Formula Three Times for One Day

These volunteers were monitored or followed up for the occurrence of any side effects or adverse reactions following the administration of the specified doses of S. argel tablets. None of the volunteers complained of blurred vision, dryness of the mouth, change in heart beats (tachycardia or bradycardia), palpitation, headache or vomiting during the period of the trial. Only one of these patients complained of dryness of the mouth and another patient complained of stomach upset felt at the time of administration of the leaves tablets. None of the participants complained of any other side effects. Furthermore, no side effects were recorded in these subjects on using Solenostemma argel herb as a medicine for a week. These observations and findings indicated the very high tolerability of Solenostemma argel tablets, of the different formulae, as no signs of adverse reactions or side effects were recorded when these tablets were administered in the doses stated. After being diagnosed, these patients were treated by using two tablets of Solenostemma argel leaves or extracts to be administered when necessary. The patients treated with S. argel tablets were followed up for the therapeutic effectiveness of the administered tablets as indicated by suppression of the symptoms, and relief of pain and colics, as well as being monitored for occurrence of side effects or adverse reactions. When necessary, another two-tablet dose was administered to patients when there was recurrence of pain, colics and other symptoms. In i.e., two tablets were administered three times daily, half an hour before meals.

The general observation in treatment of gastrointestinal disturbances with S. argel tablets was the quick suppression of symptoms and relief of pain occurring immediately following drug administration. However, in the case of renal colics, pain associated with menstrual disturbances, and irritable bowel syndrome, IBS, there might be a need for repetition of the treatment. The pain was relieved without any pronounced side effects or adverse reactions.

In the case of the patients' gastrointestinal disturbances and spasm, the pain was relieved completely.
all these patients (25, 100%); in the patients with pain associated with menstrual cycle, the pain was relieved in most patients (18, 90%); in patients with renal colics, pain was relieved in 11 patients (73%); while in 72% of the patients with IBS, pain was completely relieved. No side effects or adverse reactions were recorded, and the patients did not complain of any undesirable or intolerable toxic or adverse effects of these preparations of Solenostemma argel.

Therefore, it could be concluded that the different types (leaves, extracts or alkaloids) of Solenostemma argel tablets showed a very good therapeutic effectiveness (71%-100%), and a great margin of safety (98%-100%). These findings are very promising, but they need further confirmation in larger clinical trials involving more centres and larger numbers of clinicians and involving larger numbers of patients, as well as investigation of more experimental variables.

Therapeutic Effectiveness of Solenostemma argel Leaves, Extracts and Alkaloids Tablets Administered to Patients

Table 2: Patients participating in the Clinical Trials Involving Administration of Solenostemma argel Leaves, Extracts or Alkaloids Tablets

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Condition of Pain</th>
<th>No. of Patients</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Severe</td>
<td>40</td>
<td>Irritable Bowel Syndrome IBS</td>
</tr>
<tr>
<td>30</td>
<td>Moderate</td>
<td>25</td>
<td>Gastrointestinal Colics</td>
</tr>
<tr>
<td>45</td>
<td>Mild</td>
<td>20</td>
<td>Menstrual Disturbances</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>15</td>
<td>Renal Colics</td>
</tr>
</tbody>
</table>

*: minimum dose two leaves tablets or one-to-two extract tablets when necessary, up to two leaves tablets or one-to-two extract tablets four times a day

CONCLUSION:

The chloroform extract (600 - 800 mg) of solenostemma argel induced a delayed and gradual decrease in amplitude of the spontaneous contractions of pregnant or non-pregnant uterus. Also, there is antibiotic substances in the ethanol extracts of Hargel plant. And the presence of Kampferol and Steroidal glycosides in leaves of hargel, also there is protein, sugar, fiber, and vitamins are present with minerals Na+, K+, Ca2+, Mg2+, Ni3+, P+3 and there is occurrence of four new pregnant glycosides from the preearp of Solenostemma argel. The presence of biologically active components such as phytates and phenolic compounds are found to have adverse effects on intrinsic properties of protein. The tannins are phenolic polymers precipitate protein from aqueous solution and it is reduce or inhibit enzyme activity. Phytic acid represents a complex class of naturally occurring organic form of phosphorus compounds that can significantly influence the functional and nutritional properties of foods. Finally from this study we concluded that solenostemma argel is The data collected indicated that the medicinal herb most commonly used as a remedy for gastrointestinal disturbances was Solenostemma argel (used by 48% of the participants) compared to another four medicinal plants. The popularity of Solenostemma argel leaves in Sudan and its very wide usage as an antispasmodic in its decoction or in powder form were the motivation and persuasio to make a detailed multidisciplinary investigation of all aspects pertinent to the design, formulation and evaluation of a suitable and stable dosage form of Solenostemma argel leaves as powder, extract or alkaloids. Furthermore, surveillance of the available antispasmodic drugs showed the limitation of the high cost of some of the available products, or the common side effects and possible adverse reactions of others, e.g. dryness of the mouth and blurred vision. These observations further motivated and encouraged this work to be planned and conducted. In addition, success of this project and implementation of its findings may pave the way for other projects to be designed for further utilization of other useful medicinal plants used in folkloric practice.

REFERENCES: