ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

THE IMPORTANCE OF ADONIS HERB IN THE TREATMENT OF CARDIOVASCULAR FAILURE

E.D.Raimberdiyev , S.A.Kamolova, T.Kh.Sherov, Ch.J. Botirova

Student of Tashkent Medical Academy

Abstract: Adonis aestivalis (summer pheasant-eye) is an annual plant with a crimson flower, distributed in southern Europe and Asia. The plant has large buttercup-like blossoms and soft, fern-like leaves. It blooms in spring and is often found as a weed in cereal fields. Like other Adonis spp., the plant produces cardiac glycosides. It is used in remedies for mild weakness of the heart, especially when accompanied by nervous complaints. Cardiovascular and toxic effects of a hydroalcoholic extract from the aerial parts of A. aestivalis were investigated in sheep and mice. Six male sheep were anesthetized with sodium pentobarbital and arterial blood pressure was measured with a transducer connected to the left femoral artery. Heart rate and electrocardiogram (ECG) were registered from lead base-apex ECG derivatives connected to a Powerlab recorder. Three successive equal doses (75 mg kg-1) of the hydroalcoholic extract of A. aestivalis intravenously administered to anesthetized sheep. Adonis aestivalis extract induced a significant bradycardia and hypotension in sheep. Various ECG abnormalities in sheep included sinus arrhythmia, shortened and depressed S-T interval, and absence of P wave and flattened or inverted T wave. In addition, ventricular arrhythmias, bradyarrhythmias, atrioventricular block, ventricular premature beats, ventricular tachycardia and ventricular fibrillation have also been observed. The acute intraperitoneal toxicity (LD50) of the extract in mice was 2150 mg kg-1. In conclusion, bradycardia and ECG alterations induced by the extract could explain the justification of traditional use of the of Adonis aestivalis in treating cardiovascular insufficiency.

Key words: Adonis aestivalis, Cardiac arrhythmias, Electrocardiogram, LD5.

INTRODUCTION;

Plants have the ability to synthesize a wide variety of chemical compounds that are used to perform important biological functions, the recent reviews showed that, although plants possessed wide range of pharmacological activities and can be utilize to maintain disease-free healthy life, but they were not free from toxicity . Adonis aestivalis (summer pheasant's eye) is an annual plant with herbaceous growth. Although Adonis aestivalis has lower concentrations of cardiac glycosides than the false hellebore (A. vernalis), it remains a poisonous plant and should only be used medicinally under medical supervision . This review was designed to shed light on chemical constituents,pharmacological and

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

toxicological effects of Adonis aestivalis.

MATERIALS AND METHODS;

As well as two reviews published by Kooti et al. (2016, 2018), in this review we searched the information on this genus from databases (using Elsevier, ACS, Springer, Wiley, Nature, RSC, Medline Plus, Bentham Science, Hindawi Science, CNKI, VIP, Web of Science, Google Scholar and Baidu Scholar) and libraries, and the search languages were set to English and Chinese. We didn't set the time period for searching more literatures. The keywords were searched as Adonis for English literatures, Cejinzhan (An external file that holds a picture, illustration, etc.

Object name is fphar-10-00025-i001.jpg) and/or Fushoucao (An external file that holds a picture, illustration, etc.

Object name is fphar-10-00025-i002.jpg) for Chinese literatures. Three experts collected the literatures.

The fresh and uncrushed aerial parts of A. aestivalis were collected in West Azerbaijan county (Urmia), Iran and were authenticated at Taxonomy Unit, Basic Science College of Tarbiat Modares University, Tehran, Iran. Whole plants were dried and ground in a hammer mill then were soaked in 70% ethanol and kept at room temperature for seven days. To complete extraction, it was mixed twice daily. This procedure was repeated four times and combined ethanolic extract was evaporated to dryness on a rotary evaporator maintaining the temperature between 45 and 50 ˚C, and a deep dark brown semi-solid residue was obtained. The pure A. aestavalis hydroalcoholic extract (AAHE) was kept protected from light in a refrigerator at 4 ˚C. We found out that the yield of extract was about 9.25%. The extract was dissolved in saline for evaluation of biological activities.

Animals. The experimental protocol was approved by the Experimentation Ethics Committee on Animal Use of the Faculty of Veterinary Medicine, Urmia University, Urmia, Iran. Healthy albino mice of either sex, weighing 18-33 g, were obtained from Pasture Institute, Tehran, Iran. The animals were housed three per cage, and the photoperiod (light on from 06:00 to 18:00 hr), air circulation and room temperature (24 ± 1 ˚C) were controlled. All animals had free access to tap water and standard rodent diet.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Six healthy, adult, mixed breed male sheep with a mean body weight of 33 kg (range: 30 to 37 kg) were used in this study. All sheep were judged to be healthy based on physical examination, complete blood count, biochemistry profile and electrocardiographic (ECG) examination. The sheep were fed hay concentrate twice daily, and had access to water ad libitum. Animals were conditioned to remain in lateral recumbency.

Acute toxicity and behavioral activity tests in mice. Pilot tests were conducted to determine the dose rang of the extract to be administered in mice. The maximum dose of AAHE, producing no death and the minimum dose that produced 100% death were achieved. From these, appropriate concentrations of extract dissolved in saline containing 0.1, 1.6, 2.9, 3.5 and 5.0 g kg-1 of AAHE were given intraperitoneally (IP) to 6 groups of 5 mice each. The animals were observed for symptoms of toxicity and mortality within 24 to 72 hr. The LD50 was calculated based on Lorke's method.10 Observation continued for 14 days to confirm that the number of animals per dose that remained alive did not alter. The behavioral and CNS profiles scored were: spontaneous rearing and grooming, evidence of calmness and sedation, loss of writhing reflex and duration of sleep. Measurement of blood pressure (BP) and electrocardiography in anesthetized sheep. All sheep were anesthetized by first administering 30 mg kg-1 of 5% solution of sodium pentobarbital (Sigma, St. Louis, MO, USA) intravenously, followed by small supplemental doses as needed.

The left femoral artery was cannulated with poly-ethylene tubing PE-50 (Clay Adams, Parsippany, NJ, USA) filled with heparinized saline (60 IU mL-1), which was connected to a pressure transducer (Model MLT844; ADInstruments, Sydney, Australia) coupled to a bridge amplifier (Model ML224; ADInstruments, Sydney, Australia). The pressure transducers were calibrated with a medical manometer prior to each study, with the zero level set at the thoracic inlet of the laterally recumbent sheep. Mean arterial pressure (MAP) was calculated from the BP data sampled in an off-line analysis as:

Blood pressure = diastolic + [(systolic - diastolic)/3]

For continuous monitoring of the base-apex leads electrocardiogram, positive electrode of lead I (left arm) was attached to the skin of the left thorax at the fifth intercostal space immediately caudal to the olecranon, and the negative electrode (right arm) was placed on the jugular furrow in the caudal third of the left neck. The electrodes were placed using alligator clips and a gel contact, after clipping of the skin and cleaning with alcohol.11 The BP and ECG data were continuously displayed and recorded on-line on a personal computer by use of a data acquisition system (Model ML870; PowerLab, ADInstruments, Sydney, Australia) using LabChart (Version 6; ADInstruments, Sydney, Australia). Heart rate (HR) was calculated over the measurement period from a simultaneously recorded electrocardiogram.

The left jugular vein was cannulated with similar tubing to facilitate intravenous injections of the drugs and plant material. The exposed surface for the cannulation was covered with cotton wool moistened in warm saline. After completion of surgical preparations, the sheep were allowed to stabilize for 20 min without further intervention. The baseline ECG and hemodynamic parameters were obtained 5 min before AAHE injection (control group). Repeated doses (3 doses, 75 mg kg-1, iv) of AAHE were injected into the jugular vein to assess their cardiovascular effects on anesthetized sheep. Arterial blood pressure was

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

allowed to return to the resting level between injections. Changes in blood pressure were recorded as the difference between the steady state values before and the peak readings after injections.

For statistical analysis, significance differences between control and experimental groups were assessed by repeated measure ANOVA using SPSS (Version 17; SPSS Inc., Chicago, USA). Results were considered significant when $p < 0.05$. Data are expressed as mean ± standard error of mean (SEM).

Adonis amurensis Regel et Radde

Adonis chrysocyathus Hook.f. & Thomson

Adonis coerulea Maxim.

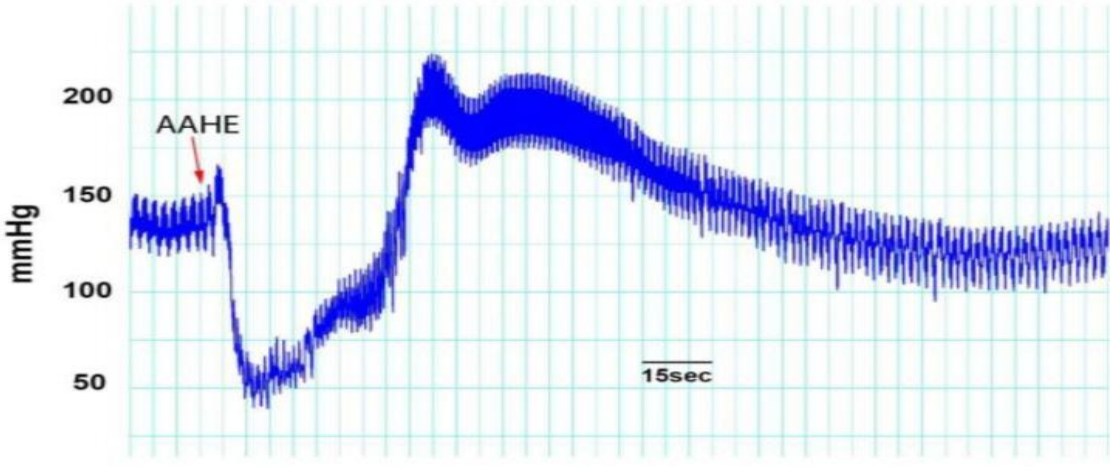
Adonis davidii Franchet

Adonis aestivalis L.

RESULTS AND DISCUSSION;

Acute toxicity in mice. The mortality rate of the intraperitoneally administered AAHE increased progressively with the increasing dose (data not shown): the mortality rate of 0% at and up to a dose of 1500 mg kg-1 gradually rose to 100% at 5000 mg kg-1, the highest dose studied. The no-observed-adverse-effect level (NOAEL) for the intraperitoneal dose was 1000 mg kg-1, while the lowest-observed-adverse-effect level (LOAEL) was 1600 mg kg-1. The severity of clinical signs was similar appreciably between individuals. Some adverse effects, such as salivation, hypo-activity, ataxia, posterior paralysis and recumbency were seen immediately after the intraperitoneal injection, while others (decreased appetite and weight loss) were observed soon after, and were more pronounced at the higher doses. Interestingly limb paralysis that leads to recumbency was resolved spontaneously later. The acute intraperitoneal toxicity (LD50) of AAHE in mice was 2150 mg kg-1. Effects of AAHE on MAP and HR. The intravenous injections of AAHE (75 mg kg-1) produced a reproducible reduction in MAP and HR. Acute administration of AAHE caused a rapid-onset decrease in MAP (Fig. 2) and HR, while the hypotensive and bradycardic effects were rather short-lived and returned toward the baseline levels within 2 to 5 min after first dose administration. A more pronounced and long-lasting response was observed at the injection of second dose and both MAP (Fig. 3) and HR remained depressed even at 5 min after AAHE administration (Fig. 4). In all of the experiments, third dose caused a rapid increase in mean blood pressure for few minutes; followed by a progressive and irreversible fall in MAP.

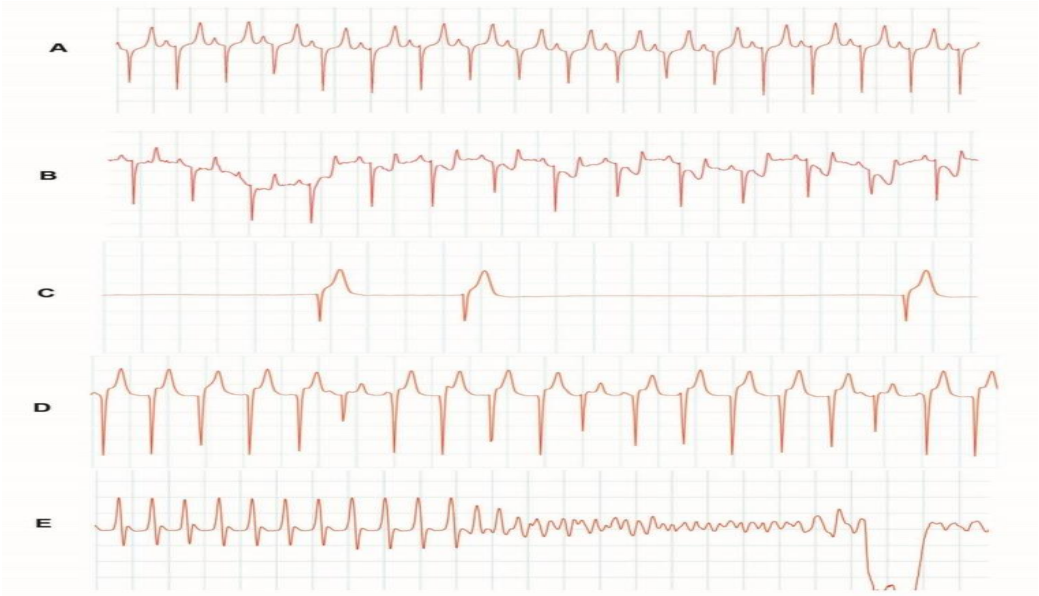
ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES



Effect of AAHE on blood pressure in anesthetized sheep.

Effects of AAHE on electrocardiogram. Heart rate was reduced 2 to 4 min after first AAHE administration significantly ($p < 0.05$). There were no significant alterations in duration and amplitude of P wave, QRS complex and T wave. P-R interval, Q-T interval and S-T segment did not show important changes during this period ($p < 0.05$). However, in all animals second dose produced a significant change in P-R and Q-T intervals. Bradycardia was replaced with pauses and tachyarrhythmias in third AAHE injection. Various ECG abnormalities observed in sheep included sinus arrhythmia, shortened and depressed S-T interval, absence of P wave and flattened or inverted T wave. Additionally, ventricular arrhythmias, bradyarrhythmias, atrioventricular (AV) block, ventricular premature beats (VPB), ventricular tachycardia (VT) and ventricular fibrillation (VF) have also been observed .

Typical ECG changes indicating arrhythmia indexes in anesthetized sheep. A. ECG before



the application of AAHE. The changes observed after the application of extract include: B. ST depression; C. Escape beats; D. Idioventricular rhythm and E. Ventricular fibrillation.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

This review highlight the chemical constituents, pharmacological and toxicological effects of A. aestivalis as a plant contains cardiovascular active metabolites. Although, it can be used therapeutically, but it remains a poisonous plant and should only be used medicinally under medical supervision.

CONCLUSION;

Because of the marked effects as a cardiotonic agent in treating heart diseases, some species of the genus Adonis L. and their extracts have been widely used clinically in some countries, including the use of A. vernalis and A. amurensis in Russia and China. To provide a comprehensive review, the information on this genus was gathered via the internet and libraries, and the search languages were set to English and Chinese. The native languages of some articles (written in Bulgarian, Russian and German) as well as other factors including older publication dates and the absence of an English abstract made it impossible for us to cite and understand some articles. Although the pharmacological effects of this plant were widely studied in Russia before 1950s, much of the relevant literature is hard to access (Shikov et al., 2014). As a result, some older studies published in various languages were not included in this review and should be examined and reviewed further. Recently, the review of botany, traditional use, phytomedicine, pharmacology and toxicity of A. vernalis provides comprehensively information for this plant used in Europe (Latté, 2018). According to the website www.theplantlist.org, 32 species from the genus were accepted as native to Europe and Asia. However, with the exception of A. vernalis, A. aestivalis, and A. amurensis, the phytochemistry and the modern pharmacology of most of the species have not been investigated comprehensively and clinically validated. Although A. vernalis has been become a well-known herbal medicine for cardioprotection, especially in Russia, Bulgaria, etc. (Popiliev et al., 1973; Sorokina, 1989; Wichtl, 1990), only small numbers of in vitro and in vivo studies on their cardioprotective effects are available (Popiliev et al., 1973). Considering that some clinical studies assayed about 50 years old are not valid anymore, the development of this genus should be paid more attention. To date, more than 120 chemical components have been isolated and identified from the genus Adonis. With the exception of the cardiac glycosides, some well-known flavones in the genus also were isolated and identified with the wide pharmacological activities, including antioxidant, anti-microbial, anti-inflammatory, cardioprotective, neuroprotective, and anti-allergic properties, and these compounds should be paid more attention (George et al., 2017; Aziz et al., 2018; Guo et al., 2018; Kim et al., 2018). Additionally, A. vernalis is a medicinal plant whose above-ground parts at the flowering or fruiting stages are harvested from the wild as a ramaterial for the pharmaceutical industry in China. In the past century, with the abundant use of A. vernalis as well as a lack of xerothermic habitats and slow plant growth among others, this resource has rapidly decreased and is close to extinction (Lange, 2000; Baier and Tischew, 2004;) Meanwhile, owing to the weak germination of the seeds and the slow growth intensity of the plants, the cultivation is unsuccessful (Galambosi, 1980a,b). Since 1982, it has been protected in several countries and the trade of this plant was banned in many East European countries (Lange, 2000). Therefore, investigation of sustainable usage practices is still necessary. This introduces the urgent problem of cultivation on a commercial scale, which would be useful for its conservation (Poluyanova and Lyubarskii, 2008). In short, the phytochemical and pharmacological studies of the genus Adonis L. have received much interest. Extracts enriched in cardiac glycosides have been developed, and active compounds have been isolated and proven to provide cardioprotective activity. However, plants of this

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

genus should be studied and developed further, with particular attention paid to conservation of resources and clinical testing.

We studied many scientific articles together with teachers and professors at the Tashkent Medical Academy. And we quoted sentences from some scientific articles. In particular, cardiac glycosides are widely used in Uzbekistan, and there are several evidences proving this. Due to the large number of medicinal plants in Uzbekistan, we believe that in the future folk medicine, i.e. oriental medicine, will be able to reach great heights.

REFERENCES;

1.X Shang · 2019 — And since the early 20th century, extracts of this plant enriched in cardiac glycosides were prepared to treat chronic heart failure in the ...

2. M Maham · 2014 — The claim of therapeutic success of the plant in the treatment of cardiovascular diseases has not been scientifically scrutinized. This prompted ...

3. KE MILLER · 2002 — ... herbal therapies. Valli and Giardina wrote a review article on the benefits, adverse effects, and drug interactions of herbal therapies that ...

4. A Shaito · 2020 — Then we overview the use of herbs for disease treatment in general and CVDs in particular. Further, data on the ethnopharmacological therapeutic potentials ...