ADONIS AESTIVALIS: PHARMACOLOGICAL AND TOXICOLOGICAL ACTIVITIES - A REVIEW

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ABSTRACT
Adonis aestivalis (summer pheasant's eye) is an annual plant with herbaceous growth. Although Adonis aestivalis has low concentrations of cardiac glycosides and it can be used therapeutically, but 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 toxicological effects of Adonis aestivalis.

Key words: Chemical constituents, pharmacology, toxicology, Adonis aestivalis.

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 [1-76]. 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 [77]. This review was designed to shed light on chemical constituents, pharmacological and toxicological effects of Adonis aestivalis.

Taxonomic classification
Kingdom: Plantae; Subkingdom: Tracheobionta; Superdivision: Spermatophyta; Division: Magnoliophyta; Class: Magnoliopsida; Subclass: Magnoliidae; Order: Ranunculales; Family: Ranunculaceae; Subfamily: Ranunculoideae Tribe: Adonideae. Genus: Adonis, Species: Adonis aestivalis [78-79].

Common names
Arabic: ain el deek, ain el booma, nab el jamal, English name: Summer Adonis and pheasant's eye, France: adonis d'été; Italian: adonide estiva; Portuguese: casadinhos, gotas-de-sangue; Russian: adonis letnii; Spanish: adonis estival, gota de sangre Swedish: sommaradonis [78-80].

Distribution
It was distributed in Europe and Mediterranean region. Adonis spp., including Adonis aestivalis (summer pheasant’s eye, summer adonis) have long been utilized in European folk medicine for their cardiac-enhancing effects. Summer pheasant’s eye was introduced into North America as a horticultural plant, escaped cultivation and is now naturalized in the western United States. There is concern that the plant may become better established in the western region of North America and may be more commonly found as a poisonous weed in hay. Recognition of summer Adonis or any other poisonous plant in hay is instrumental in preventing poisoning. Adonis spp. are members of the buttercup family (Ranunculaceae) and are considered unpalatable which is most likely the reason why reports of poisoning are rare [81]. However, the plant is distributed in Africa: Algeria; Asia: Afghanistan; Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, China and India; Europe: Austria, Czech Republic, Germany, Hungary, Poland, Slovakia, Switzerland, Russian Federation, Bosnia, Herzegovina, Bulgaria, Croatia, Greece, Italy, Macedonia; Romania; Serbia; Slovenia, France and Spain [79].

Traditional uses
Infusions of A. aestivalis are used as diuretic, spasmylytic, sleeping draught, and cough medicine. Species of Adonis are used to create medicines for stimulating heart
function. The substance used is similar to those of Digitalis (foxglove) and are often prescribed in its place, to avoid the long-term effects of digitalis-derived drugs [77, 82].

Description
Herb, annual, taprooted. Stem 1, 20-50(-100) cm. Leaves: basal leaves 3-5 cm, similar to cauline, petiolate; cauline leaves sessile or subsessile. Leaf blade 2-3-pinnatifid. Flowers 1.5-3.5 cm diam.; sepals appressed to petals, broadly obovate, ± erose in distal 1/3, minutely ciliate, otherwise glabrous; petals 6-8, ± erect, orange [yellow, scarlet, or bright red-purple], usually with dark purple basal blotch, ± plane, 10-17 mm, ca. 1.5 times length of calyx, apex slightly erose; stamens ca. 30; anthers purple-black (olive green with age); pistils 30-40. Heads of achenes cylindric, 20-30 × 7-10mm; pedicels conspicuously exerted well beyond leaves; achenes 4-6mm, glabrous, adaxial margin with low, rounded tooth, transverse flange around middle (most pronounced abaxially), abaxial keel bearing small obtuse tooth at junction with flange; beak straight, erect, 1.5-2 mm [83].

Part used: The whole herb.

Chemical constituents
The plant contained cardenolides mainly strophanthinid aglycone [84-85]. Four cardenolides were isolated for the first time from the aerial parts of Adonis aestivalis. These compounds were identified as 3-epiperiplogenin, helveticoside, strophanthinid-3-O-beta-D-digitoxosido-alpha-L-cymarosido-be ta-D-glucoside and strophanthinid-3-O-beta-D-digitoxosido-beta-D-digoxoside-beta-D-digoxosido-beta-D-glucoside [86].

Chemical investigation of the seeds of Adonis aestivalis has led to the isolation of a new cardenolide (3β,5α,14β,17β-tetrahydroxycard-20,22-enolide), two new glycosides, and a new strophanthinid hexaglycoside, together with a known compound, strophanthinid-3-O-beta-D-glucopyranoside [87].

Carotenoids and their fatty acid esters were investigated in the petals of Adonis aestivalis. (3S,3'S) - astaxanthin (diester: 72.2%, monoester: 13.8%, free: 1.4%) and (3S)-adoninurbin (monoester: 13.8%, free: 0.3%) were identified as the major components [88].

However Kamata et al., found that the total carotenoids of the flower petal of the Adonis aestivalis were 1979.88 µg/g, these included β- carotene 16.43 µg/g (0.83%), 4-hydroxyechinenone 17.62 µg/g (0.89%), 3-hydroxyechinenone 33.26 µg/g (1.68%), astaxanthin diester 1525.07 µg/g (77.02%), lutein 122.37 µg/g (6.18%), adonixanthin 104.35 µg/g (5.27%), astaxanthin 66.53 µg/g (3.36%), 3,3,4,4 tetrahydroxy β- carotene 32.47 µg/g (1.64%) and unidentified compound 61.78 µg/g (1.64%) [89].

PHARMACOLOGICAL EFFECTS
Cardiac effects

Strophanthidin aglycone is one of several cardenolides extracted from Adonis aestivalis. The direct effect elicited by these compounds is similar to other cardiac glycoside-containing plants and is due to inhibition of the sodium potassium adenosine triphosphatase enzyme system pump. They increase vagal tone, which decreases the rate of sinoatrial node depolarization. In intoxication, the electro-cardiographic changes seen are include bradycardia, varying levels of atrio-ventricular block, ventricular arrhythmias, and ventricular fibrillation [90-91].

Tincture of Adonis vernalis is used by homeopathic physicians in patients suffering from congestive cardiac failure. Its action was very much similar to digitalis on heart. Aqueous extract of Adonis vernalis was found to have cardiac stimulant action on isolated heart preparations. It showed protection against heart failure produced by excessive load and high potassium concentration. Tincture of Adonis vernalis was found to cause cardiac depression which was not blocked by the atropine. In isolated guinea pig and rabbit auricles the drug increased the threshold of electrical stimulation. The dog blood pressure responses was varied with dose, low doses showed rise in blood pressure whereas larger doses showed fall in blood pressure [92].

Cytotoxic effects
Cardenolide compounds, isolated from the seeds of Adonis aestivalis, were examined for their cytotoxic activity against neoplastic HSC-2, HSC-3, HSC-4, and HL-60 cells, as well as HGF, HPLF, and HPC normal cell lines. Three of five cardenolide compounds isolated from the seeds of Adonis aestivalis were found to display selective cytotoxicity toward malignant tumor cell lines. Although the morphological observations of HL-60 and HSC-2 cell deaths revealed changes characteristic of apoptosis, neither DNA degradation nor activation of caspase-3 was observed. The findings demonstrated that these compounds may trigger caspase-3-independent apoptotic cell death in HL-60 and HSC-2 cells [87].

Antilithiatic activity
The antilithiatic activity of extracts of dried leaves and roots powder of Adonis aestivalis was proven in rat [93].

Using of A. aestivalis as a pigment
It was well established that certain species of Adonis flower such as Adonis aestivalis contained astaxanthin as a major pigment. According to Neamtu et al., more than 80% of the total pigments in Adonis aestivalis was astaxanthin, mostly in the ester form. Their results suggested that this flower could be used for salmonids as a pigment source. The coloration of salmonids and crustaceans has become of interest in the cultivation of these species as an important factor affecting consumer acceptance [94].
The flower, *Adonis aestivalis* and its pigment extract were fed to two different sizes of rainbow trout *Salmo gairdneri* at a level of 10mg total pigment/100g diet. The larger fish (average weight 400g) were fed the pigment extract for 8 weeks. In the males, carotenoids were mainly deposited in the skin and a small amount was found in the flesh. However, in the females, a relatively high level of carotenoids was detected in the flesh. The smaller fish were fed the diets containing Adonis flower petals or its pigment extract. After two weeks of feeding, the Adonis flower group discontinued feeding activity and mortalities ensued. However, no mortalities resulted in the Adonis extract group over a three month feeding period, and a noticeable pink coloration was observed in the skin of this group [89].

**Toxicity**

*Adonis* poisoning has been reported in horses, pigs, calves, rabbits and sheep. Plants of the *Adonis* genus contain cardiac glycosides similar to the toxins present in oleander and foxglove [84-85, 95-98].

Due to natural exposure to *Adonis* spp, acute poisonings have been reported in horses. Clinical signs of summer adonis poisoning in horses include gastrointestinal disturbances, such as colic, hemorrhagic enteritis, diarrhea or decreased gut motility. In addition, the cardiotoxins present in *Adonis* can lead to a variety of cardiac arrhythmias and death [95].

Intoxicated horses showed gastrointestinal stasis and myocardial degeneration after ingestion of *Adonis aestivalis*-contaminated hay. Endocardial hemorrhage and gaseous distension of the gastrointestinal tract were the only necropsy findings. Microscopic examination showed scattered foci of mild, acute myocardial necrosis and neutrophilic inflammation associated with endocardial and epicardial hemorrhage. *Adonis aestivalis* was identified in the hay. Strophanthidin, the aglycone of several cardenolides present in *Adonis* spp., was detected by liquid chromatography-mass spectrometry in gastrointestinal contents of the intoxicated horses [95, 99-100]. *Adonis aestivalis* intoxication was also recorded in the pigs. The signs and symptoms of intoxication in pigs fed a diet containing seeds of *Adonis* spp were include feed refusal, vomiting, dyspnea, and death [96].

Sheep did not develop clinical signs when dosed with 1 per cent bodyweight ground adonis (estimated content 11 to 17 ppm strophanthinid) via rumen cannulas, or when dosed daily for two weeks with 0.2 per cent bodyweight adonis per day. Extensive cardiac examinations demonstrated transient cardiac functional effects. No gross or microscopic lesions were evident in the heart or any other tissues examined [85].

However, cardiovascular and toxic effects of a hydroalcoholic extract from the aerial parts of *A. aestivalis* (AAHE) 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) 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 [101].

Calves fed 0.2 to 1% body weight *Adonis* spp daily for 4 to 5 weeks complained transient, mild cardiac abnormalities during the feeding trial. Mild, transient gastrointestinal and cardiac signs were noted in the pre-ruminating calves. No gross or microscopic lesions were seen on necropsies performed at the end of the study [79].

Microscopical examination of rabbits tissues experimentally intoxicated with *A. aestivalis* showed severe hemorrhage, myocardial degeneration and necrosis in cardiac cells, severe congestion and swelling of hepatocytes in liver, spread interstitial alveolar edema, congestion of pulmonary arteries, medial hyperplasia and emphysema in lungs, PVC (pre-vascular cuffing), chromatolysis, neurophagy and focal glosis in brain, severe swelling of tubular endothelial cells, congestion of glomeruli, hyaline casts and severe tubular necrosis in kidney, papillary hyperplasia of mucus layer, and mucous secretions into the intestine lumen were also observed [98].

In mice, the mortality rate of the intra-peritoneally administered hydroalcoholic extract from the aerial parts of *A. aestivalis* (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 gradually rose to 100% at 5000 mg/kg, the highest dose studied. The no-observed-adverse-effect level (NOAEL) for the intraperitoneal dose was 1000 mg/kg, while the lowest-observed-adverse-effect level (LOAEL) was 1600 mg/kg. 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 *A. aestivalis* hydroalcoholic extract (AAHE) in mice was 2150 mg/kg [101].

**CONCLUSION**

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.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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