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**Mini Review**

# Inventory of poisonings and toxicological studies carried out on *Atractylis gummifera* L.: A review

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**Summary**
*Atractylis gummifera* L. belongs to the family Asteraceae is widely used in traditional Moroccan medicine for its therapeutic effects (diuretic, purgative, emetic, abortive), but it causes serious and fatal poisonings, hence the objective of this work is to describe the current state of intoxication caused by *A. gummifera* in the Mediterranean and to summarize the toxicological studies carried out on this plant. The working methodology we adopted consisted in collecting data published in Arabic, French and English in specialized articles, books and on websites. Research results showed that the Centre Anti Poison and Pharmacovigilance of Morocco declared *A. gummifera* was in second place in the occurrence of poisonings in between January 1980 and December 2008. The synthesis of experimental work on plant toxicology showed that the lethal dose of *A. gummifera* varies according to the animal model used (rat or mouse), the route of administration (intraperitoneal, oral or intravenous) and the part of the plant used. The root has been found to be the most toxic part of the plant. The toxicity of *A. gummifera* is due to atractyloside and gummiferine, which are inhibitors of oxidative phosphorylation that prevent the formation of ATP from ADP in intracellular organelles. This study shows the interest in raising public awareness of the toxicity of *A. gummifera* and in rationalizing its use in traditional medicine.

**Keywords:** *Atractylis gummifera*; Intoxication; Toxicological study; Atractyloside; Carboxyatractyloside

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## Introduction

Over the years, man has learned to recognize plants and exploit them for nutritional, cosmetic or even decorative purposes. Also, he made this floristic heritage an important therapeutic source that is implanted in medicinal traditions.

Morocco, with its 7000 plant species, is a true phytotherapy reservoir that allows it to occupy

a privileged place among the countries around the Mediterranean region which have a long medicinal culture and ancestral herbal know-how (1, 2). However, several of these medicinal plants are the origin of poisonings, which are accidental most of the time and sometimes happen voluntary, thus constituting a rather serious public health problem (3, 4). In this respect, the World Health Organization (WHO) estimates that 80% of the world's population uses plants as primary health care methods, which increases the risk of poisoning by plants (5, 6).

Indeed, several plants around the Mediterranean have therapeutic uses, but they can cause serious poisoning if they are not used properly (3). Hence, the need to study these plants and conducts phytochemical, pharmacological and toxicological studies are a pressing necessity to rationalize their use.

*Peganum harmala* L. is one of the most toxic plants, but widely used in traditional medicine for its many therapeutic virtues, and our laboratory is interested in this plant and endorsed it chemically and pharmacologically for its biological activities *in vitro* and *in vivo* and also by identifying the therapeutic doses of toxic doses (7- 11).

The *Asteraceae* family is one of the most widely used plant families in phytotherapy both in Morocco and in other Mediterranean countries (12-14), but it is also considered one of the richest families in toxic species (15). *Atractylis gummifera* L. which carries many more other botanical synonyms which are summarized in Table 1 (16). The systematic classification of this plant is given in Table 2 (17). This plant has several vernacular names; which change from one region to another (Arabic, French, English and Italian). Most of these vernacular names are summarized in Table 3 with its proper citations. (16, 18-26).

This plant is very abundant in the Mediterranean region, particularly in southern Europe, Italy, Greece, Spain, Portugal, France and North Africa (27-29).

Also, *Artemisia herba-alba* and *Artemisia arborescens* are among the *Asteraceae* that have a very remarkable therapeutic value and are very used despite their intense toxicity (15). These plants are widely used for their effects on digestive system, diabetes, gastrointestinal antiseptic, anthelmintic, diuretic, an aperitif, colds, and vertigo. However, these plants can cause very serious poisoning like dizziness and convulsions disorders (15, 18, 27).

**Table 1.** Botanical synonyms of *Atractylis gummifera* L.

| | |
|---|---|
| Botanical synonyms | *Atractylis gummifera* L. |
| | *Carlina gummifera* DC. |
| | *Carlina gummifera* Less. |
| | *Acarna gummifera* Brot. |
| | *Acarna gummifera* Willd. |

**Table 2.** Systematic classification of *Atractylis gummifera* L.

| | |
|---|---|
| Kingdom | Plants |
| Branch line | Embryophytes |
| Clade | Angiosperms |
| Clade | Dicotyledons |
| Order | *Asterales* |
| Family | *Asteraceae* |
| Genus | *Atractylis* |
| Species | *Atractylis gummifera* L. |

**Table 3.** Vernacular names of *Atractylis gummifera* L.

| | Countries | Vernacular name | References |
|---|---|---|---|
| Arabic names | Morocco | *Chouk el heulk, El-'alk* | (16) |
| | Algeria | *Djerniz, Leddad, Addad, Chouk el alek, Suk el-'alk* | (18-20) |
| | Tunisia | *Dâd, Ded, Edded, Haddad* | (21) |
| Amazigh names | Morocco | *Âhfyûn*, Addâd, H*addad* | (22-24) |
| | Algeria | *Adad, Tifroua, Tabonekkart* | (25, 26) |
| | Tunisia | *Âddâd, Ddâd* | (18) |
| French names | *Chardon à glu, Caméléon blanc, Chamaeléon blanc, Carthame gummifère* | | (16) |
| English names | *Bird-lime, Glue thistl* | | (3) |
| Italian name | *Masticogna* | | (3) |

## Description of *Atractylis gummifera*

*A. gummifera* is a herbaceous, thorny and perennial herb. It has leaves that form a rosette at ground level and are dry and thorny form a defensive mat. Its stem is reduced or unapparent from which tears flow, which constitute a kind of glue, from where the name Glue thistle came (Fig. 1 & 2). The flowers are pink, purple or pinkish purple and remain long enough after the leaves have dried out. They appear in summer, between June and July (Fig. 3). The underground part of this plant (Fig. 4) consists of a bulky rhizome that can reach 30 to 40 centimeters long and 7 to 8 centimeters wide; it is very hard, fibrous and yellowish in color. The rhizome is attached to a long root that allows the plant to maintain itself for many years (27, 29).

## Traditional use of *A. gummifera*

In Morocco, *A. gummifera* is one of the most used herbs in alternative medicine (3), particularly in the treatment of edemas, psoriasis and epilepsy, to stop hemorrhages and facilitate childbirth (30-33).

## Pharmacological property of *A. gummifera*

In addition, this plant has a beneficial effect on the trapping of free radicals which are triggers of several metabolic diseases such as diabetes (34), and the prevention against oxidative stress because its aqueous and methanolic extracts have

**Fig. 1.** *Atractylis gummifera* L.: Whole plant

**Fig. 2.** Aerial part of *Atractylis gummifera* L.

**Fig. 3.** Flower of *Atractylis gummifera* L.

**Fig. 4.** Underground part of *Atractylis gummifera* L. (Rhizome)

- Pictures taken by Khadija Bouabid on 20/04/2019.
- The plant is harvested in the commune of Tahla, province of Taza region of Fez - Meknes, Morocco.
- Coordinates: 34° 03 N, 4° 25 W.
- Geographical habitat: Species from the Mediterranean region.

the capacity to reduce the radical DPPH and to inhibit the reducing power of iron (35). Also, we have shown in our previous works that the extracts of *A. gummifera* prepared by aqueous and methanolic macerations of the underground part of this plant are very rich in phenolic compounds, flavonoids and tannins and are capable of inhibiting the key enzymes responsible for the degradation of polysaccharides: alpha amylase, alpha glucosidase and beta galactosidase (36). The study of the acute toxicity of these two extracts (aqueous and methanolic macerations of the underground part of *A. gummifera*) on Albino-Souis mice allowed us to determine their lethal doses 50 ($LD_{50}$) which proved to be superior at 2g / kg. Based on this result, we have chosen for the *in vivo* study of the antidiabetic activity of the both macerates of *A. gummifera* the therapeutic doses of 500mg/kg which are significantly lower than the toxic dose for treating diabetic mice. Thus, we have demonstrated that our extracts have the ability to lower blood sugar levels in these mice and reduce the level of biochemical parameters to normal such as: aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), urea, creatinine, cholesterol, triglycerides and total proteins (37). In addition, it was recently shown in an Algerian study carried out by Mejdoub and his collaborators in 2019 that essential oils extracted from the underground part of *Atractylis gummifera* in full bloom had interesting antioxidant and antifungal properties, while those produced at the beginning of the vegetative cycle (March) and at the beginning of flowering (April) had better insecticidal activity (38). Despite the frequent traditional use of Glue thistle, it is one of the main causes of plant poisoning caused by the ingestion of the mostly fresh root and often fatal (15, 27, 39).

The objective of this work is to make an inventory of the poisonings caused by *A. gummifera* in the Mediterranean region and a synthesis of the experimental work carried out on the toxicity of this plant.

## Search strategies

The methodology adopted in this study is based on the collection of information relating to toxicological studies and data about poisoning by *A. gummifera*, by doing bibliographic researches using the following keywords: *Atractylis gummifera*; Poisoning; Toxicological study; Atractyloside; Carboxyatractyloside, in order to search for pertinent publications indexed in the database of the Institute for Scientific Information (Thomson Scientific), PubMed, Scopus, Google Scholar and Science Direct. Several articles were obtained by this bibliographic research and we have included in this study in addition to the documents published in English, those published in Arabic and French. The Fig. 5 illustrates how the articles were selected for the final analysis.

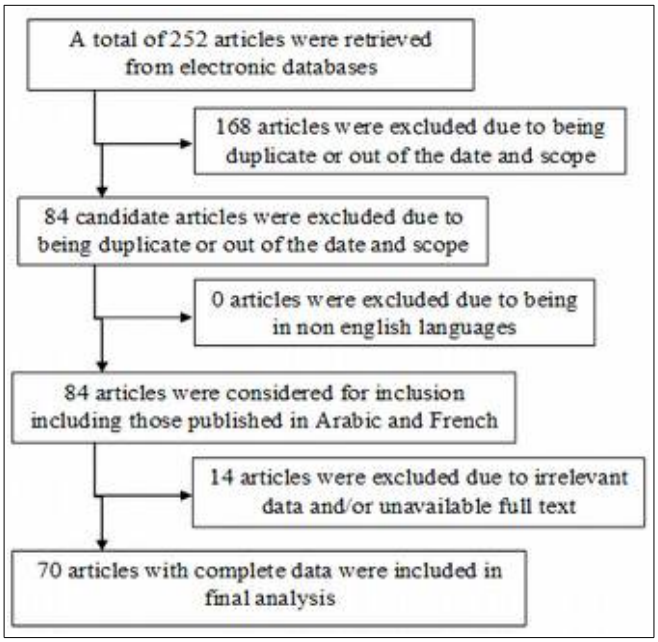


**Fig. 5.** Flowchart of the process of selecting the articles for final analysis

## Results and Discussion

### Inventory of poisoning caused by *A. gummifera* in the Mediterranean region

The ingestion of plants as products of the traditional pharmacopoeia or as food products or even contact with plants can cause real problems that affect human health. Among these plants, *A. gummifera*, one of the plants that is often implicated in several cases of severe poisoning reported especially in spring and summer; flowering period of this plant, 72% of the victims of which were children under 16 years old (40-44). There are three principal causes of poisoning by this plant:

- The principal cause of the poisoning is the use of *A. gummifera* in traditional medicine. Indeed, it has been reported in several studies that the root of *A. gummifera* is much used, principally by women to tan the skin, in the treatment of oedema, psoriasis, boils, and epilepsy for stopping hemorrhages, facilitating childbirth and also for its abortive properties (30-33). The root of *A. gummifera* is also used in ritual fumigations against evil geniuses and the evil eye (45).

- The second cause of poisoning by *A. gummifera* is the accidental exposition due to an error in the identification of this plant and its confusion with other edible plants, such as the Spanish artichoke (*Scolymus hispanicus*) (40).

- The poisoning may also be due to criminal exposition because of the facility to obtain the toxic at any time and in any place, it's not very marked taste, it's easy dissimulation in food and its almost certain and rapid results, as well as the difficulty to prove its use by poisoners. Also, intoxication can be suicidal by ingestion of the plant alone or associated with certain drugs (39-41).

Data published by the Moroccan Anti-Poison and Pharmacovigilance Center on poisoning by *A. gummifera* from 1980 to 2009. According to it, a study realized over a period of 15 years (January 1980 - June 1995), had reported 153 cases of *A. gummifera* poisoning with three peaks: 1985 with 20 cases, 1988 with 20 cases and 22 cases in 1993. Also, it was reported according to the same center that 461 cases of poisoning were reported between 1980 and 2009 with a fatality rate of 24.1% (42, 46-50).

In Algeria, the report of the Centre Anti-Poison, reveals that this plant is the first among the plants responsible of poisoning between 1991 and 2009 that is 10% of the poisoning by plants are due to *A. gummifera* (1554 cases). Deaths due to poisoning by this plant, over the same period, represent 15% of total deaths (51).

In Tunisia, among the 56 cases of plant poisoning registered in the Toxicology and Intensive Care Unit of Tunis between 1983 and 1998, 32% were due to the ingestion of *A. gummifera* with 16 cases of death (52).

In the northern Mediterranean countries (Spain, Portugal, Italy, France), there is a great diversity of plants, 200 of which are considered toxic. However, very few poisoning by these plants have been noted (5%) because the population is generally aware of the toxicity of the plants. These intoxications essentially concern children (65%), as they can be due to a suicidal act, or confusion with another plant (53). Table 4 summarizes toxicity data of *A. gummifera*.

**Table 4:** Toxicity data of *Atractylis gummifera* L.

| Countries | Time period | Number of poisoning cases | Total deaths |
|---|---|---|---|
| Morocco | Between 1980 and 2009 | 461 | 24.1% |
| Algeria | Between 1991 and 2009 | 1554 | 17.5% |
| Tunisia | Between 1983 and 1998 | 56 | 32.0% |

The poisoning by *A. gummifera* is manifested by two clinical forms. The first form is benign, short-term, and consists of digestive disorders, without neurological damage, while the second form of poisoning is severe and often fatal (54). It is dominated by fulminate hepatitis, hypertonic coma and marked hypoglycemia. Renal, hematological and cardiovascular damage, as well as biological perturbations can be observed. In the absence of a specific antidote, treatment is initiated by perfusion of glucose-serum followed by gastric lavage and symptomatic treatment (54-56).

### Synthesis of experimental work carried out on the toxicology of *A. gummifera*

The various toxicology studies conducted on *A. gummifera* have shown that the toxicity of this plant depends on the dose of the toxicant, the route it is administered and the animal model used (15, 57, 58). Based on these variables, the researchers were able to determine the lethal dose of this plant. Table 5 summarizes the variation in lethal dose 50 ($LD_{50}$). According to the toxic substance, the animal model was used and also the route of administration.

Thus, we can see that the variation in the $LD_{50}$ depends essentially on the part of the plant material used and its passage into the general bloodstream. Indeed, absorption is often influenced by the route of administration, where the intravenous route is the route where the entire administered dose reaches the systemic circulation. Thus, we noted that in all studies, the $LD_{50}$ remains very small when the toxicant is administered intraperitoneally. It is injected directly into the abdomen, unlike the oral route

**Table 5**. Lethal doses of *Atractylis gummifera* L.

| Plant material / Toxic substances | Animal model | Route of administration | Lethal dose 50 ($LD_{50}$) | Reference |
|---|---|---|---|---|
| Underground part of *A. gummifera* | Mice | Intraperitoneal | $LD_{50}$= 101.5 mg/kg | (56) |
| Underground part of *A. gummifera* | Mice | Oral | $LD_{50}$ > 2000mg/kg | (37) |
| Atractyloside | Rat | Intraperitoneal | $LD_{50}$= 143 mg/kg | (57) |
| Carboxyatractyloside | Rat | Intraperitoneal | $LD_{50}$ = 2.9 mg/kg | (58) |
| Atractyloside | Rat | Oral | $LD_{50}$= 1000 mg/kg | (59) |
| Carboxyatractyloside | Rat | Oral | $LD_{50}$ = 350 mg/kg | (60) |

where the $LD_{50}$ is characterized by higher values, the toxicant passes through several steps before reaching the bloodstream, causing its degradation and metabolism. This explains the results of our study (37) where the $LD_{50}$ was greater than 2000mg/kg orally in mice; we also noted a total absence of any signs of toxicity at this same dose.

In addition, it has been shown that the substances responsible for the toxic effects of *A. gummifera* are two diterpenic heteroglycosides, the first being called atractyloside or atractyline (ATR) (Fig. 6) and was isolated in 1868 by Lefranc (64), and the second is carboxyatractyloside or gummiferine, identified in 1964 by Danieli and his collaborators (CATR) (Fig. 7) (65), it is a homologous of atractyloside but of much greater toxicity.

The mechanism of action of these heteroglycosides is the inhibition of the transport of phosphorylated nucleotides through the mitochondrial membrane, which prevents mitochondrial oxidative phosphorylation and disrupts tissue respiration by blocking the tricarboxylic acid cycle (Krebs cycle) (66). This inhibition is ten times higher by carboxyatractyloside than atractyloside due to the presence of the second C4 acid function of Atractyloside (67).

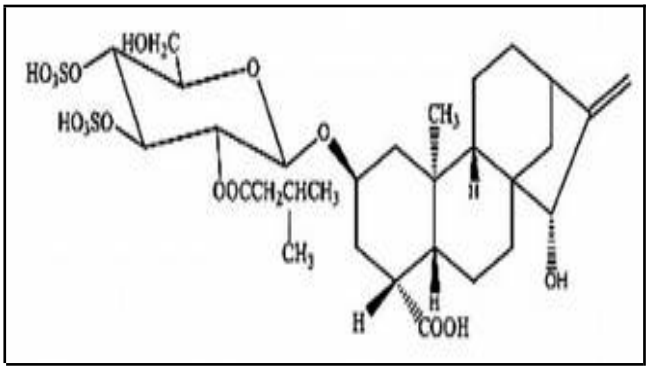


**Fig. 6.** Atractyloside structure (64)

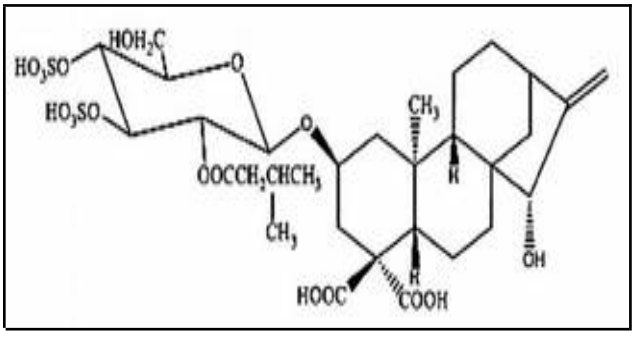


**Fig. 7.** Carboxyatractyloside structure (65)

However, it is imperative to point out that these heterosides are naturally present in many other plants, some of which are used in phytomedcine or for food purposes, such as dried *Coffea arabica* beans, which are widely present in human diets at a concentration of 17.5 mg/kg, which shows the importance of a broader risk to humans since there is no data to identify the risk of chronic exposure at low doses in human coffee consumers (66).

The identification of atractyloside can be done by colorimetric reactions using usual reagents. Such as, the reaction with Froedhe's reagent (sulfomolybdic) which gives a yellow-orange coloring in the presence of atractyloside and the addition of water causes this solution to change from yellow-orange to stable violet (67-69). All parts of *Atractylis gummifera* contain atractyloside and gummiferin but with values that vary according to the organs of this plant. Indeed, the rhizome contains the highest toxic content followed by the stem, bracts, flower and seed and finally the leaf that contains the least (70).

## Conclusion

The plants have always been an important source for the treatment of various diseases. However, their uses must be readjusted in order to benefit only from their therapeutic effects and avoid their toxic effects.

*Atractylis gummifera* L. is one of the plants that is largely used traditionally, but also causes serious to fatal poisoning. Indeed, the synthesis of bibliographic data on this plant indicated that 461 cases were reported between 1980 and 2009 with a fatality rate of 24.1% in Morocco.

In Algeria, *A. gummifera* is in the second place with 17.50% cases of poisoning. In Tunisia, 32% of poisoning cases were due to *A. gummifera*

between 1983 and 1998. Moreover, the synthesis of the experimental work on toxicological studies realized on *A. gummifera* indicated that the lethal dose of this plant depends on the route of administration and the animal model used and that the toxicity of this plant is due to two glycosides: Atractyloside and Carboxyatractyloside.

## Authors' contribution

KB has done the collection of literature, took photos of the plant in the field and laboratory and prepared the manuscript. FL designed the manuscript, participated in data collection and article preparation, corrected the manuscript and edited the final version and submitted it for publication, HT and MEAF helped to improve the manuscript and participated in the correction of the manuscript. All the authors approved the final manuscript.

## Competing interest statement

The authors declare no conflict of interest.

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