A Systematic and Mechanistic Review on the Phytopharmacological Properties of Alhagi Species

Abstract

Alhagi species are well known in Iran (locally known as Khar Shotor) and other parts of Asia as a popular folk medicine. Recent research has shown extensive pharmacological effects of these species. This paper is a comprehensive review of the phytopharmacological effects and traditional uses of Alhagi species and their active constituents with special attention to the responsible mechanisms, effective dosages and routes of administration. The Alhagi species studied in this paper include: A. maurorum, A. camelorum, A. persarum, A. pseudoalhagi, and A. kirgisorum. In order to include all the up to date data, the authors went through several databases including the Web of Science, Embase, etc. The findings were critically reviewed and sorted on the basis of relevance to the topic. Tables have been used to clearly present the ideas and discrepancies were settled through discussion. Alhagi species have significant biomedical properties which can be exploited in clinical use. Proanthocyanidin isolated from A. pseudoalhagi has significant biochemical effects on blood factors. Among Alhagi species, A. camelorum and A. maurorum possess the highest anti-microbial activity. Most of the effects observed with A. maurorum are dose-dependent. This paper indicates with emphasis that Alhagi species are safe and rich sources of biologically active compounds with low toxicity. Since DNA damage has been observed following the ingestion of specific concentrations of A. pseudalhagi, care should be taken during administration of the plant for therapeutic use. Further studies are required to confirm the safety and quality of these plants to be used by clinicians as therapeutic agents.

Keywords: A. camelorum, A. persarum, Alhagi maurorum, folk medicine, mechanistic review

Introduction

The genus Alhagi includes a number of species, the most important of which are A. maurorum, A. camelorum, and A. persarum. To the best of our knowledge, this is the first and the most inclusive review paper prepared so far, regarding the traditional usages and pharmacological effects of Alhagi species [Tables 1 and 2] with special emphasis on the mechanisms involved [Table 3]. We have compiled the most effective dosages responsible for each effect based on previous pharmacological studies. This is to provide a reliable source for other researchers. The findings were critically reviewed and sorted on the basis of relevance to the topic. Tables were used to clearly present the ideas and discrepancies were settled through discussion.

Approach to Systematic Review

An online literature search was performed on Web of science, Embase, PubMed, and Google Scholar databases for the key words of Alhagi, pharmacol, etc., with a time limit of papers published from 2004 up to November 2015 in accordance to PRISMA guidelines. The search strategy is illustrated in a flow diagram [Figure 1].

Gastrointestinal Effects

Local inhabitants of India use A. maurorum to cure stomach and intestinal complaints including diarrhea, dyspepsia, constipation, bloating, diminished appetite and also for the treatment of liver inflammation. Major chemical compounds found in A. maurorum are β-sitosterol, cinnamic acid, coumaric acid, hydroxybenzoic acid,[14] In Arabian traditional medicine A. maurorum is used for the prevention and treatment of liver ailments (such as jaundice), lack of appetite, nausea, vomiting and other stomach disorders. A study on the ethno-veterinary usage of A. camelorum of Greater Cholistan desert of Pakistan

Address for correspondence:
Dr. Milad Moloudizargarī, Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, 2Department of Pharmacology, Faculty of Medicine, Urmia University of Medical Sciences, 3Department of Pharmacy, Faculty of Veterinary Medicine, Urmia University, Urmia, 4Department of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran.

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indicated that *A. camelorum* has aperient properties in animals.\[14\] Investigations on the hepato-protective effect of *A. maurorum* showed that Ethanolic Extract of this plant at the doses of 250 and 500 mg/kg failed to inhibit the raised biomarkers (SGOT, SGPT, ALP and bilirubin levels).\[15\]

### Anti-inflammatory Effects

One study showed that the aqueous extract of *A. maurorum* may be useful in protection against inflammatory diseases, especially if free radicals are a part of its pathophysiology. The extract significantly reduced the thickness of paw edema induced by formalin in a dose-dependent manner.\[17\] It has been shown that *A. maurorum* Medic is a more potent anti-inflammatory agent in comparison to diclofenac sodium (30 mg/kg), a conventional anti-inflammatory drug.\[21\]

### Antioxidant Effects

The aqueous extract of *A. maurorum* exerts antioxidant effects by reducing malondialdehyde levels.\[17\] The alcoholic extract of *A. maurorum* Medic has also shown antioxidant activity by scavenging free radicals at different concentrations (2, 4, 6, 8 and 10 mg/ml).\[21\] The leaf extract has higher antioxidant potential than the flower extract due to its higher phenolic contents.\[22\] Three important antioxidant flavonoids have been isolated from

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### Table 1: Traditional uses of *Alhagi* species

| System               | Species          | Effect                              | Preparation               | References |
|----------------------|------------------|-------------------------------------|---------------------------|------------|
| Systemic             | *A. maurorum*    | Anti-toxic against mercury toxicity | Juice                     | [1]        |
|                     | *A. maurorum*    | Anti-rheumatism                     | Oil from leaves           | [1-3]      |
|                     | *A. camelorum*   | Diaphoretic                         |                           |            |
|                     | *A. maurorum*    | Against warts                       | NM                        | [2]        |
|                     | *A. graecorum*   | Antipyretic, antiviral, antimicrobial, | Decoction, soak          | [4,5]      |
|                     | *A. maurorum*    | demulcent, and adaptogen            |                           |            |
|                     | *A. camelorum*   | Antipyretic                         | NM                        | [3]        |
|                     | *A. graecorum*   | Thirst                              | Soak                      | [4]        |
| Blood                | *A. maurorum*    | Purifies blood                      | NM                        | [1]        |
|                     | *A. maurorum*    | Against bleeding piles              | Decoction                 | [1,2]      |
|                     | *A. graecorum*   | Jaundice                            | sox                       | [4]        |
| Urinary system       | *A. maurorum*    | Diuretic                            | Decoction, soak           | [1,2,4]    |
|                     | *A. camelorum*   | Diuretic                            | Infusion of leaves        | [3,6]      |
|                     | *A. persarum*    | Controls pH of urine (veterinary use) |                           | [2]        |
|                     | *A. maurorum*    | Bladder infection                   | Boiled and brewed, infusion of leaves | [6,7] |
|                     | *A. persarum*    |                                        |                           |            |
|                     | *A. camelorum*   | Exertion of kidney stones           | Infusion, decoction       | [6,8,9]    |
|                     | *A. persarum*    |                                        |                           |            |
| Gastrointestinal     | *A. maurorum*    | Purgative                           | Exudation (leaves and branches) | [1,2,4,10]|
|                     | *A. graecorum*   | Purgative                           | Soak                      | [4]        |
|                     | *A. maurorum*    | To treat gastric ulcer, heartburn and gastric efflux | Aqueous extract | [2]        |
|                     | *A. graecorum*   | Intestinal infection                | Boiled and brewed         | [7]        |
|                     | *A. maurorum*    | Appetite suppressant                | Decoction, soak           | [4]        |
|                     | *A. persarum*    | Pregnancy constipation              | NM                        | [11]       |
|                     | *A. persarum*    |                                        |                           |            |
| Skin                 | *A. maurorum*    | Against skin eruption               | Decoction                 | [1]        |
|                     | *A. graecorum*   | Aphthous ulcers                     | sox                       | [4]        |
|                     | *A. persarum*    | Skin wounds, skin irritations, allergic rashes, and dermatitis | Galenical | [12]       |
| CNS                  | *A. maurorum*    | Against migraine                    | NM                        | [2]        |
|                     | *A. maurorum*    | Cold headache (nasal administration) | Leaves (nasal drops)      | [13]       |

NM: Not mentioned, *A. maurorum*: *Alhagi maurorum*, *A. kirgisorum*: *Alhagi kirgisorum*, *A. camelorum*: *Alhagi camelorum*, CNS: Central nervous system
Table 2: Pharmacological effects of Alhagi species

| System          | Species          | Effect                                               | Preparation         | References |
|-----------------|------------------|------------------------------------------------------|---------------------|------------|
| Gastrointestinal| *A. maurorum*    | Curing stomach and intestinal complaints and liver ailments | Ethanolic extract   | [14,15]    |
|                 | *A. camelorum*   | Aperient properties                                 | Extract             | [16]       |
|                 | *A. maurorum*    | Anti-inflammatory (reduces the thickness of paw edema) | Aqueous extract     | [17]       |
|                 | *A. maurorum*    | Antidiarrheal (increases contractile force of duodenal smooth muscles) | Methanolic extract | [18]       |
|                 | *A. maurorum*    | Antidiarrheal (in low concentration: Increases the contractile force in high concentration: possesses rapid sedative effect) | Methanolic extract | [9]        |
|                 | *A. camelorum*   | Anti-ulcerogenic (decreases acid output)            | Ethanolic extract   | [20]       |
| Systemic        | *A. maurorum*    | Anti-oxidant (reduces malondialdehyde levels)       | Aqueous extract     | [17]       |
|                 | *A. maurorum*    | Anti-oxidant (scavenging free radicals)             | Alcoholic extract   | [21]       |
|                 | *A. maurorum*    | Anti-oxidant (scavenging free radicals)             | Methanolic extract  | [22]       |
|                 | *A. pseudoalhagi*| Anti-tumor (increases immune activity)               | Extract             | [23]       |
| Urinary tract   | *A. persarum*    | Diuretic, antilithiatic                              | Extract             | [6]        |
|                 | *A. camelorum*   | Treatment of kidney pain                             | Extract             | [19]       |
|                 | *A. maurorum*    | Getting rid of renal stones and relieve of the accompanying pain | Ethanolic extract   | [24]       |
|                 | *A. pseudoalhagi*| Diuretic, reduction of the urine PH and crystalluria | Extract             | [25]       |
| Antimicrobial    | *A. camelorum*   | Anti-bacterial (against *S. aureus*)                 | Methanolic extract  | [26]       |
|                 | *A. maurorum*    | Anti-bacterial (against *E. coli*)                   | Methanolic extract  | [27]       |
|                 | *A. maurorum*    | Anti-bacterial (against Helicobacter)                | Methanolic extract  | [28]       |
|                 | *A. maurorum*    | Anti-fungal (against *A. alternata, F. oxysporum, P. destructiva, R. solani, and S. rolfsii*) | Ethanolic extract   | [29]       |
| Blood           | *A. pseudoalhagi*| Decreases bilirubin levels                           | Extract             | [30]       |
|                 | *A. pseudoalhagi*| Decreases serum creatinine phosphate level and lipid peroxidation | Extract             | [31]       |
|                 | *A. kirgisorum S*| Inhibits protein synthesis in reticulocytes          | Phenolic compound   | [32]       |
| CNS             | *A. maurorum*    | Anti-noceptive (central analgesic activity)          | Extract             | [33]       |
|                 | *A. maurorum*    | Anti-noceptive (protection against writhing)         | Ethanolic extract   | [21]       |
|                 | *A. maurorum*    | Anti-noceptive (in accordance with its traditional use) | Methanolic extract  | [9]        |
| Genome          | *A. pseudoalhagi*| Genotoxicity (causes DNA damage at a concentration of 5 µg/ml) | Extract             | [34]       |

* A. pseudoalhagi: *Alhagi pseudoalhagi*, *A. maurorum*: *Alhagi maurorum*, *A. kirgisorum*: *Alhagi kirgisorum*, *A. camelorum*: *Alhagi camelorum*, *A. alternate*: *Alternaria alternate*, *F. oxysporum*: *Fusarium oxysporum*, *P. destructiva*: *Phoma destructiva*, *R. solani*: *Rhizoctonia solani*, *S. rolfsii*: *Sclerotium rolfsii*, *E. coli*: *Escherichia coli*, *S. aureus*: *Staphylococcus aureus*, CNS: Central nervous system

*A. maurorum* which include isorhamnetin-3-O- [- alpha-l-rhamnopyranosyl- (1-3)- beta- D-gluco pyranoside, 3’-O-methylorobol and Quercetin 3-O-beta-d-gluco pyranoside. [37]

**Urinary Tract Effects**

In Iranian traditional medicine, a glass of *A. persarum* is taken before meals to treat urinary tract infections. It is also used as an effective diuretic and anti-lithiastic agent. [6] An ethno-pharmacological survey in the north of Iran showed that the concentrated decoction of *A. camelorum* was used among Iranians for the treatment of kidney pain. [19] It was shown in a study that the ethanolic extract of the roots of *A. maurorum* possesses spasmylytic and ureter relaxing activity. It is also effective in relieving the pain resulting from renal stones (contraction of the ureter). [24] The same anti-lithiastic effect has been elicited from 2% aqueous acetic acid extract of *A. maurorum* powdered roots. [38] In addition to its diuretic effect, *A. pseudoalhagi* can reliably reduce the urine pH for a long time. This species of *Alhagi* also has the potential to reduce crystalluria. [23]

**Anti-microbial Effects**

*A. camelorum* has been long used by native Iranians in the treatment of infectious diseases. [27] A study indicates that the methanolic extract of *A. camelorum* has antibacterial activity against *Staphylococcus aureus*, supporting its traditional use by Iranians. Methanolic extract of *A. maurorum* used in folklore Iranian medicine has antibacterial activity against two strain of *Escherichia coli* at a concentration of 20 mgmL⁻¹. [26]

In an *in vitro* study on the anti-helicobacter activity of some Egyptian plants, the extracts of *A. maurorum* exhibited the strongest activity. This effect of the plant was assessed after determination of its MIC by agar diffusion method. [28]
Table 3: Detailed presentation of some previously proven phyto-pharmacological properties of *Alhagi* species

| Species     | Model     | Activity                               | Preparation   | Exposure duration | Type of administration | Doses          | Outcomes                                                                 | References |
|-------------|-----------|----------------------------------------|---------------|------------------|------------------------|----------------|---------------------------------------------------------------------------|------------|
| *A. maurorum* | *In vivo*/*rabbit* | Hepatoprotective                        | Aqueous-ethanol extract | 7 days           | P.O.                   | 250 mg/kg, 500 mg/kg | ↓ALP, ↓SGOT, ↓SGPT, ↓TB, ↓Fatty degeneration in hepatocytes               | [35]       |
| *A. maurorum* | *In vivo*/*mice* | Anti-inflammatory, analgesic, antioxidant and antibacterial | Aqueous Extract | 1 day            | P.O.                   | 125 µg/animal, 250 µg/animal, 500 µg/animal | A dose-dependent reduction in the growth of edema, decrease in frequency of licking of the formalin-injected paw, no antibacterial activity | [17]       |
|             |           |                                        |               |                  |                        |                | A dose-dependent reduction in the growth of edema, decrease in frequency of licking of the formalin-injected paw, ↑total antioxidant capacity, no antibacterial activity |           |
| *A. maurorum* | *In vitro*/*HL-60* | Antimicrobial and cytotoxic             | Methanol extract | Up to 72 h       | -                      | 100, 200, 400 µg/ml, 10, 50, 100 µg/ml | ↑antimicrobial activity, Antioxidant activity: ↑Free radical scavenging activity and ↓LPO at dose of 100; A dose-dependent inhibition of xanthine oxidase | [36]       |
|             |           |                                        |               |                  |                        |                | Cytotoxic activity: ↑cytotoxic activities in HL-60 cell line, ↓antiproliferative activity on HL-60 cell |           |
| *A. maurorum* | *In vivo*/*rat* | Anti-inflammatory and anti-ulcer activity | Ethanol extract | 2 times through the 10 days | Orally                | 100 mg/kg     | ↓MDA level, ↑GSH level, ↓cholesterol-LDL                                     | [20]       |

ALP: Alkaline phosphatase, SGOT: Serum glutamic oxalacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, TB: Total bilirubin, MDA: Malondialdehyde, HL-60: Human leukemia cell line, LPO: Lipid peroxidation, GSH: Glutathione
Another in vitro study in Saudi Arabia on the anti-fungal activity of *A. maurorum* showed that the ethanolic extract of this plant is effective against *Alternaria alternata*, *Fusarium oxysporum*, *Phoma destructiva*, *Rhizoctonia solani*, and *Sclerotium rolfsii* at a concentration of 9%.[29]

**Biochemical Effects**

An in vitro study revealed that *A. pseudalhagi* extract may decrease bilirubin levels by cathartic effect or activation of liver enzymes.[30] Another study showed that intravenous administration of proantocyanidin isolated from *A. pseudalhagi* diminishes serum creatinine phosphate levels and lipid peroxidation both in the myocardium and serum in animals with experimental myocardial infarction.[31] A survey in 1990 indicated that a phenolic compound from *A. kirgisorum* S. (Polyproanthocyanidin) impressively inhibited protein synthesis in rabbit reticulocyte.[32] *A. camelorum* also has therapeutic potential in the treatment of diabetes and other chronic diseases. The suggested mechanism of action is α-Glucosidase inhibition.[33]

**Anti-diarrhoecal Effects**

*A. maurorum* and a concentrated decoction of *A. camelorum* have been used in traditional medicine of Egypt and Iran for the treatment of diarrhea.[9,19] In an in vitro study, methanol extract of the aerial parts of *A. maurorum* at a dose of 200 mg/kg (IP) exhibited a significant anti-diarrheal effect against castor oil-induced diarrhea, and also increased the contractile force of duodenal smooth muscles in rabbits.[18] In another study it was shown that the oral administration of the extract can exert anti-diarrheal effects as well. The suggested mechanism of action in low concentrations (0.4 mg/ml) is increasing the contractile force. Higher concentrations (3.2 mg/ml) caused a rapid sedative effect. The sedative effect induced by *A. maurorum* (at higher doses) appeared to be due to calcium channel blocking effect.[19]

**Anti-ulcerogenic Effects**

In one study, six main flavonoid glycosides were isolated from the ethanol extract of *A. maurorum*. The flavonoids were identified as kaempferol, chrysoeriol, isorhamnetin, chrysoeriol-7-O-xyllosoid, kaempferol-3-galactorhamnoside and isorhamnetin3-O-b-D-apio-furanosyl (1-2) b-D-galactopyranoside. The total extract (300 and 400 mg/kg) and two of the isolated compounds (chrysoeriol 7-O-xyllosoid and kaempferol-3-galactorhamnoside, 100 mg/kg each) showed a very promising anti-ulcerogenic activity with curative ratios of 66.31%, 69.57%, 75.49%, and 77.93%, respectively.[19] It was also shown that the ethanolic extract of *A. maurorum* in combination with ranitidine can be used in rats to protect them against the side effects of aspirin administered two times through 10 days. Decreased acid output as a result of the plant extract and ranitidine administration was suggested as the mechanism responsible for this effect.[20]

**Anti-tumoral Effects**

Abnormal Savda Munziq (ASMq), a traditional Uyghur medicinal herbal preparation from the Xinjiang region of China, has long been used in Traditional Uyghur Medicine for the treatment of complex diseases such as tumors. ASMq is composed of ten medicinal herbs one of which is *A. pseudalhagi*. The anti-tumour activity of this compound has been pharmacologically proven with a suggested mechanism of increasing immune activity.[40]

**Anti-nociceptive Effects**

*A. maurorum* has been traditionally used by Egyptians to relieve pain.[9] The plant has been shown to possess central analgesic effect at the dose of 500 mg/kg. This activity is mediated through opioidergic receptors.[33] In one study, ethanol extracts of *A. maurorum* Medic was shown to exert significant protection against writhing.[21]

**Genotoxicity**

*A. pseudalhagi* which has been long used by traditional Iranians has been shown to cause DNA damage at a concentration of 5 µg/ml, and a concentration less than 5 µg/ml is proven to be safe.[31]
Implications in Traditional Medicine

A multitude of preparations made from *Alhagi* species have been acknowledged in [Iranian] traditional medicine. These preparations have been beneficial in treating a number of disorders involving different systems. *A. maurorum* has been used in the treatment of gastric ulcers,[19] intestinal tract infections,[19] as an expectorant,[2] appetite suppressant[14] and as a purgative.[14,20] *A. camelorum* and *A. persarum* also have been used in ameliorating pregnancy constipation.[11] In dermatologic conditions, *A. maurorum*, *A. graceum* and *A. persarum* have been applied on skin eruptions,[14] aphthous ulcers[14] and skin wounds and inflammations[12] respectively. Interestingly, *A. maurorum* has antimigraine properties[2] and has been further administered nasally to soothe headache due to colds.[13] In the urinary system, *A. maurorum*, *A. camelorum* and *A. persarum* can cause diuresis[1,4,6] and aid in passing renal stones.[6,8,9] In addition, boiled infusions of *A. maurorum* and *A. persarum* act as a urinary disinfectant.[6,7] Moreover, *A. maurorum* is proven to be protective in various other conditions such as, mercury poisoning and rheumatism[1,13] and is active against microbial and viral organisms.[2,4,5] These enormous therapeutic effects of *Alhagi* species indicate their great potential as traditional remedies and should inspire researchers to further investigate this marvelous genus.

Conclusion

Our aim of conducting this study was to present a compilation of evidence-based comprehensive information regarding the traditional usage of *Alhagi* species with special attention to their previously proven pharmacological effects and mechanisms. Since there are a vast number of studies in the literature conducted on *Alhagi* species, this paper can provide almost all the required information as a comprehensive reference for further studies that might be performed by other researchers in the future. As it is evident from this study, *Alhagi* species possess a wide range of pharmacological effects, the most important of which include: gastrointestinal, antioxidant, anti-inflammatory, and antimicrobial effects among many others. These species have been traditionally used for renal stones, stomach complaints, to relieve pain, and to reduce paw edema in veterinary medicine, etc, Proantocyanidin isolated from *A. pseudalhagi* has significant biochemical effects on blood factors. Among *Alhagi* species, *A. camelorum* and *A. maurorum* possess the highest anti-microbial activity. Most of the effects observed with *A. maurorum* have had a dose-dependent behaviour. The doses at which the best effects have been recorded in different systems following the administration of *A. maurorum*, ranged between 100 to 500 mg/kg for in vivo studies. Since DNA damage has been observed following the ingestion of specific concentrations of *A. pseudalhagi*, care should be taken during administration of the plant for therapeutic use. A vast number of pharmacological and medicinal properties of *Alhagi* species make these plants a desirable source for development of new drugs; however, more studies are required to be conducted to specify the precise quality and safety of the plants to be further used by clinicians and other healthcare professionals for therapeutic purposes.

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Conflicts of interest

There are no conflicts of interest.

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