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Phytochemistry and ethnopharmacology of parasitic plant Cuscuta reflexa: A review

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Abstract
Medicinal plants have played an important role in treating and preventing a verity of diseases throughout the world. Bangladesh still depends on medicinal plants and most of them have general medicinal plants which are used for treating a verity of ailments. *Cuscuta reflexa* belongs to the family of Convolvulaceae. The aim of the resent study was to evaluate a comprehensive review on the phytochemical and pharmacological aspects of *Cuscuta reflexa*. It has been investigated for hepatoprotective, antimicrobial, antitumor, wound healing, hypoglycemic, anti-HIV, diuretic, anticonvulsant, anti-inflammatory and anticancer activities. Many chemical constituents have been isolated from *Cuscuta reflexa* such as cuscutin, cuscutamine, kaempferol, quercetin, myricetin, amarbelin, *β*-sitosterol, ararbelin, luteolin, dulcitrol, cafferi acid.

Keywords: kaempferol, quercetin, myricetin, amarbelin, β-sitosterol, ararbelin, luteolin, dulcitrol, cafferi acid

Introduction
Unani and Ayurvedic medicines mainly based on plants enjoy a respective position today, especially in the developing countries, where modern health services are limited. Safe effective and inexpensive indigenous remedies are gaining popularity among the people of both urban and rural areas especially in Bangladesh. *Cuscuta reflexa* (Convolvulaceae) also known as Swaranlata, Devils guts, Hair weed and Love-wine [1]. It is a leafless, delicate yellow colored total stem parasite and found throughout in Bangladesh. The species are rootless, leafless twining annual parasites with yellowish stems, distributed across tropical and temperate regions, and in India about 6 species are found. It grows on thorny or other shrubs, sometimes completely covering bushes and trees [2]. *Cuscuta reflexa* spread from one host to another, and on each victim, they twine and cling tightly with special branching organs called houstoria, penetrating the host and connecting to the host xylem as well as to the host phloem, and absorbing from it both water and elaborated food stuffs such as sugars and amino acids[3]. Various parts of the plant have been traditionally used to treat a wide range of ailments. Seeds from the plant are known to have a carminative and purgative effect, whilst the juice can be used as an anthelmintic or as a detoxifier to purify the blood [4]. Further, a fruit decoction can be imbibed to treat a cough and fever and the stem can be ingested for the alleviation of constipation, flatulence and liver complaints [5].

Synonyms

Tamil	: Verillakothan
English	: Dodder Plant
Hindi	: Amarabela
Sanscrit	: Akasavalli, Amaravalli, Khavalli
Punjabi	: Zarbut
Malayalam	: Moodillathali
Urdu	: Akashbel
Bengali	: Akashbel

Fig 1: *Cuscuta reflexa*

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Scientific classification

Kingdom	- Plantae
Subkingdom	- Tracheobionta
Superdivision	- Spermatophyta
Division	- Angiospermes
Class	- Eudicots
Subclass	- Asterids
Order	- Solanales
Family	- Cuscutaceae alternate Covolvulaceae - Dodder
Genus	- Cuscuta
Species	- reflexa Roxb. 100-170 Species Available

Phytoconstituents

The chemical constituents of *Cuscuta reflexa* are dulcitol, mannitol, sitosterol, carotenoids, flavonoids, isorhamnetin-3-O-neohesperidoside, apigenin-7-*β*-rutinoside, lycopene, 6,7-dimethoxy coumarin (scoparone), 6-hydroxy-4-(4-hydroxyphenyl)-7-methoxy-coumarin, quercetin, hyperoside [6], apigenin-7-O-glucoside, kaempferol-3-O-α-rhamnoside, myricetin-3-O-α-rhamnoside [7], 7′-(3′,4′-hydroxyphenyl)-N- [(4-methoxyphenyl) ethyl] propionamide, 7′-(4′-hydroxy, 3′-methoxyphenyl)-N- [(4-butylphenyl)ethyl] propenamide [8], reflexin [9], violaxanthin, lutein, lycopene, carotene, α-cryptoxanthin [10], amarbelin, cerotic, linolenic, oleic, stearic, and palmitic acids, phytosterols (seeds), abscisic acid (leaves), leuteolin and its glycosides [11], quercetin, cuscutin (stem), amino acids and cuscutalin [12]. Seeds also contain the esters of higher aliphatic alcohol with the saturated fatty acids respectively containing 26 and 28 carbon atoms among which cerotic acid has been identified [10]. Phytochemical analysis of phanerogamic parasite *Cuscuta reflexa* showed that it mainly contained caffeic acid depsides and flavonol type flavonoids. Some phenolic constituents were also reported [13]. The immobilization of *Cuscuta reflexa* starch phosphorylase was carried out for production of glucose-1-phosphate by using the bioreactors [14]. Choudhury *et al* [15] reviewed photosynthetic properties of *Cuscuta* species such as chloroplast, ultra structure contents of chlorophyll, carotenoids and plastid proteins, photo system and carbon dioxide fixation activities and photosynthetic genes composition.

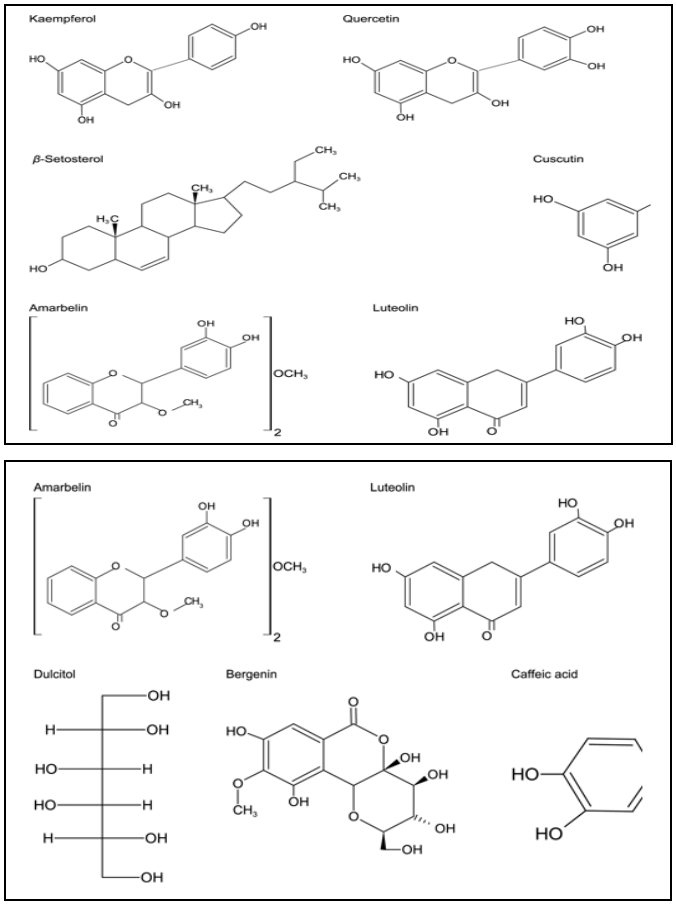

Fig 2: Phytochemical constituents of *Cuscuta reflexa*

Pharmacological Activity

Hepatoprotective activity

Hepatoprotective activity with alcoholic extracts of stem of *Cuscuta reflexa* and aqueous extracts of stem of *Cuscuta reflexa* was studied against paracetamol induced hepatotoxicity in rats. Functional (thiopentone induced sleeping time), physical (wet liver weight and volume), biochemical parameters Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Serum alkaline phosphatase (ALP), Serum direct bilirubin (BILD), Serum total bilirubin (BILT), Serum albumin (ALB), Serum total proteins (PRO), Serum cholesterol (CHO), and histopathological changes of livers were assessed in control/toxicant/standard/and extract treated animals with paracetamol induced hepatotoxic models in rats. In LD_{50} studies for AESCR and AQESCR up to the maximum dose level of 2000 mg/kg dose no mortality was observed in any of the animals, indicating the practically nontoxic. When compared to toxicant control groups both the extracts have significantly reduced the paracetamol induced elevated levels of serum ALT, AST, ALP, BILT, BILD, CHO, and elevated the levels of ALB and PRO. The histopathological changes (steatosis), necrosis etc. were partly or fully prevented in animals treated with the two extracts. AESCR and AQESCR showed a significant hepatoprotective effect against paracetamol induced hepatic damage. The medium and high doses of AESCR and AQESCR (200 and 400 mg/kg) treated groups showd better hepatoprotective activity when compared to standard drug silymarin (25 mg/kg) [16].

The methanolic extract of the stem of *Cuscuta reflexa* was evaluated for hepatoprotective activity by observing its effects on carbon tetrachloride (CCl_4) induced hepatotoxicity in liver histoarchitecture and alteration in certain biochemical parameters. The biochemical parameters studied were aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin and total protein. The crude extract was administered through the intraperitonial route in two dose groups, a lower dose group receiving 5mg/kg body weight/day and a higher dose group receiving 10mg/kg body weight/day. The study was carried out using Swiss albino mice of either sex, the weight of which ranged from 20-40 gm. The results that were compared with Silymarin, which was used as a standard to ascertain the presence of hepatoprotective activity in the methanolic extract of the stem of the said plant. The crude extract administration led to reversal of the altered biochemical parameters in the group receiving the higher dose. Also, significant alterations of CCl_4-induced changes in the histoarchitecture of the liver cells were observed in the same. Both the doses of test drug i.e. methanolic extract (direct) of *Cuscuta reflexa* (Roxb.) were effective in lowering different elevated serum parameters like AST, ALT, ALP, total protein and bilirubin. In comparison with the standard drug Silymarin, the higher test group (TGB) i.e. the group receiving the extract at a dose of 10mg/kg/day intraperitonially showed better efficacy in lowering the aforesaid parameters with respect to the group receiving the test drug at a lower dose (TGA) of 5mg/kg [17].

In vivo hepatoprotective activity of the Cuscuta reflexa whole plant extract was carried out using carbon tetrachloride, ethanol and paracetamol induced hepatotoxic rat models and compared with silymarin (20 mg/kg) as reference standard. Least significant difference test of various biochemical parameters have indicated the highest dose of aqueous extract (200 mg/kg) was having comparable hepatoprotective activity to that of standard silymarin, which was also evident from the histopathological study of liver sections. However, activity of aqueous extracts of Cuscuta reflexa whole plant (100 mg/kg and 200 mg/kg) were statistically not comparable (p-value < 0.05) with their respective SL treated standard groups [18].

Antimicrobial activity

Ethanolic whole plant extracts obtained from *Cuscuta reflexa* were screened against Gram positive (Bacillus subtilis and Staphylococcus aureus) and Gram negative (Escherichia coli and Salmonella typhi) bacteria to evaluate their antimicrobial activity. Of the four concentrations of plant extract tested (200 µg/mL, 300 µg/mL, 400 µg/mL or 500 µg/mL), 500 µg/mL elicited the greatest zones of bacterial inhibition across three of the bacteria. In contrast, the growth of Salmonella typhi was not halted regardless of extract concentration. At 200 µg/mL, only the growth of E. coli was inhibited. Overall, although the greatest antimicrobial activity was demonstrated to be against E. coli at a concentration of 500 µg/mL (24.6±0.24), upon comparison to the other bacteria, both B. cereus and S. aureus educed similar zones of inhibition upon comparison to their positive antibiotic control [19].

Antitumor Activity

The antitumor activity of the chloroform and ethanol extracts of Cuscuta reflexa was evaluated against Ehrlich ascites carcinoma (EAC) tumor in mice at doses of 200 and 400 mg/kg body weight orally, respectively, while acute oral toxicity studies were performed to determine the safety of the extracts. Briefly, the EAC cells were injected (i.p.) into ninty six mice (divided into 6 numerically equal groups), and after a one-day incubation period, the extracts were administered to the mice daily for 16 days. On day 21, six animals in each group were sacrificed for observation of antitumor activity and the remaining animals were observed to determine host the life span. Antitumor effect was determined by evaluating tumor volume, viable and nonviable tumor cell count and hematological parameters of the host. The standard antitumor used was 5-fluorouracil. Administration of the extracts resulted in a significant ($p < 0.05$) decrease in tumor volume and viable cell count, but increased non-viable cell count and mean survival time, thereby increasing the life span of the tumor-bearing mice. Restoration of hematological parameters - red blood cells (RBC), hemoglobin, white blood cells (WBC) and lymphocyte count - to normal levels in extract-treated mice was also observed. The results suggest that the chloroform and ethanol extracts of Cuscuta reflexa exhibit significant antitumor activity in EAC-bearing mice that is comparable to that of the reference standard, 5fluorouracil [20].

Wound healing activity

Wound healing activity was to investigate the properties of 0.5 mg concentration of 50% of methanol extract of Cuscuta reflexa which contains the active compound flavonoids and compared their anti-inflammatory effect with betadine, a commercial synthetic drug. The rate of wound healing and re-epithelization of the methanolic extract of this weed was found better than betadine. The mean value of wound contraction of both anterior and posterior site of control and experiment group was taken at 5th, 10th, 15th, 20th day [21].

Hypoglycemic effects

The hypoglycemic effects of methanol and chloroform extracts of whole plants of Cuscuta reflexa, investigated in oral glucose tolerance tests in Long Evans rats and Swiss albino mice, respectively. Both methanol and chloroform extracts of Cuscuta reflexa whole plant demonstrated significant oral hypoglycemic activity in glucose-loaded rats at doses of 50, 100 and 200 mg/kg body weight. When tested at doses of 100 and 250 mg/kg body weight did not demonstrate any oral hypoglycemic effect when tested in glucose-loaded mice.Cuscuta reflexa contains a number of compounds like flavonoids (kaempferol, quercitin), coumarins, and flavonoid glycosides. Earlier studies have shown that both kaempferol and quercetin could significantly improve insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes. It was further reported that these two

compounds act at multiple targets to ameliorate hyperglycemia [22].

Effect on blood pressure

The alcoholic extract of this plant has positive inotropic and cardiotonic activities on the perfuse frog heart. In a series of experiments on dog blood pressure, it caused a fall in blood pressure. This depressor action was not blocked by atropine, mepyramine or propranolol, thus it could not be exerted through cholinergic, histaminergic or adrenergic mechanisms. Although the site of action remains to be elucidated, the possibility of action on the ganglia cannot be excluded [26]. An ethanolic extract of the stem of *C. reflexa* caused a dose-dependent decrease in arterial blood pressure and heart rate in pentothal-anaesthetized rats, and these effects were not blocked by atropine. Hypotensive and bradycardiac effects of *Cuscuta reflexa* were found to be independent of cholinergic receptor stimulation or adrenergic blockade [23].

Anti-HIV activity

The crude water extracts of *Cuscuta reflexa* exhibited anti-HIV activity that could be due to combinatory effects with compounds of different modes of action [24].

Diuretic activity

The aqueous and alcoholic extracts of *Cuscuta reflexa* have diuretic activities in Wistar rat [25].

Anticonvulsant activity

The ethanolic extract has anticonvulsant property and may probably affect both the gamma amino butyric acid (GABA) aminergic- and glycine-inhibitory mechanism. The main active chemical constituent is flavonoid which is responsible for depressant activity [26]. The methanol extract of both *Cuscuta reflexa* stem and *Corchorus olitorius* seed showed marked protection against convulsion induced by chemoconvulsive agents in mice. The catecholamine contained in the extracts was significantly increased in the processed extract-treated mice. The amount of GABA, which is most likely to be involved in seizure activity, was increased significantly in mice brain after a six-week treatment. The processed extracts showed a significant anticonvulsive property by altering the levels of catecholamine and brain amino acids in mice [27].

Anti-inflammatory and anticancer activities

Cuscuta reflexa inhibited lipopolysaccharide-induced inflammatory responses in RAW264.7 cells (mouse macrophage cell) through interplay of tumour necrosis factor-α, cyclooxygenase 2 and nuclear factor κB signalling. It induced apoptosis in Hep3B cells (human hepatoma cell) through the up-regulation of p53, B-cell lymphoma 2 (Bcl-2)-associated X protein and down regulation of Bcl-2 and surviving [28]. The chloroform and ethanol extracts of *Cuscuta reflexa* exhibited a significant antitumor activity in Ehrlich ascites carcinoma-bearing mice that is comparable to that of the reference standard, 5-fluorouracil [29].

Conclusions

Cuscuta reflexa is a rootless, leafless perennial parasitic twining herb. It has no chlorophyll and cannot make its own food by photosynthesis. It grows on thorny or other shrubs, sometimes completely covering the bushes and trees. The plant *Cuscuta reflexa* is used for the treatment of diseases like hepatitis, wound, headache, diseases of spleen, inflammation, pain in the muscles and joints. The *Cuscuta reflexa* contain a variety of biologically active compounds such as cuscutin, cuscutamine, kaempferol, quercetin, myricetin, amarbelin, *β*-sitosterol, ararbelin, luteolin, dulcitrol, cafferi acid. This review will help to researchers to go deep in this area as plant indicate vast range of phytochemical related to origin so it can be suggested the further work can be done on *Cuscuta reflexa*.

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