Review Article

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PHARMACOLOGICAL IMPORTANCE OF BIOACTIVE MOLECULES FROM MEDICINALLY IMPORTANT PLANT PARASITE *CUSCUTA REFLEXA*: AN OVERVIEW

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ABSTRACT

Medicinal plants have been used as a resource for the treatments in local communities from ancient time. The parasitic plant *Cuscuta reflexa* also has medicinal properties. Many tribes and traditional communities use different forms of *Cuscuta reflexa* for the treatment and prevention of many diseases notably diabetes mellitus, headache, depression, mental illness, jaundice and hypertension, etc. Large numbers of phytochemical constituents such as alkaloids, flavonoids, lignins, oxygen heterocyclic compounds, steroids, fatty acids, phenolic acids, resin glycosides and polysaccharides have been isolated from *Cuscuta reflexa*. Ethnopharmacological studies conducted on such constituents have shown to have anticancer, antiviral, antihypertensive, antibacterial and antioxidant and diuretic properties. In this review, we are presenting a detailed survey on the studies of *Cuscuta reflexa* including its chemical constituents, ethno medicinal uses and pharmacological activities. This study will be encouraged for exploring new bioactive compounds with various functions which are not reported till date. To conclude, we provide evidences and new insights for further discovery and development of natural drugs from *Cuscuta reflexa* and its mechanism of action.

Keywords: *Cuscuta reflexa,* ethno medicinal, antioxidant, bioactive, pharmacological, antibacterial

INTRODUCTION

Medicinal plants

Plants have been used by mankind for thousands of years as a source of medicine to treat health disorders and to prevent diseases. Generally, plants that are commonly used for treatments of specific ailments and diseases are termed as medicinal plants[1]. The medicinal properties of some plant species are attributed to innumerable secondary/specialized metabolites (terpenoids, phenylpropanoids and alkaloids) produced by plants as part of their defense against biotic and abiotic stresses (Figure 1). At present many modern drugs have been isolated from medicinal plants for the treatment of various kinds of diseases[2]. For instance, vinblastine and vincristine from *Catharanthus roseus*[3] and taxol from *Taxus baccata*[4] are very effective in the treatment of cancer. Ajmaline and vincamine from *C. roseus* have antiarrhythmic properties[5,6]. Similarly, plant derived artemisinin obtained from *Artemisia annua* and quinine from *Cinchona* bark are potential drugs used for the treatment of malaria[7,8]. Some other important medicinal plants which are commonly used in traditional medicines are *Withania somnifera, Andrographis paniculata*, *Rauwolfia serpentina, Solanum xanthocarpum, Plumbago indica,* etc. *W. somnifera* roots and leaves are used in Ayurveda, Unani and Siddha medicines as well as in homeopathy. The pharmacological activities of the plants are attributed to the presence of steroidal lactones called withanolides[9,10]. *A. paniculata* is one of the most popular medicinal plants traditionally used for the treatment of array of diseases such as cancer, diabetes, high blood pressure, bronchitis etc. Its medicinal properties are attributed to presence of various diterpenes, flavonoids[11]. Root extracts of *R. serpentina* is used for the treatment of hypertension and insomnia and this plant is rich source of alkaloids like serpentine, ajmaline, ajmalicine, etc. Due to valuable application of secondary metabolites derived from medicinal plants, these days researchers are aiming to increase the production of these metabolites by metabolic engineering or through traditional plant breeding.

Cuscuta reflexa

Cuscuta reflexa Roxb. (Dodder) belongs to the family convolvulaceae and commonly known as 'Amarbel' in India, is a golden yellow green stem holoparasitic plant. It is widely distributed throughout India[12,13]. *Cuscuta reflexa* is mainly found in the temperate and tropical region of the world. The genus *Cuscuta* contains about more than 100 species which are parasite to many trees, shrubs, herbs and affect commercially valuable plants. *Cuscuta reflexa* is a leafless and rootless parasitic plant. The leafless stem coils around the host stems and petioles is able to grow on plenty of different host plants to obtain nutrients and water. Monocot crops are less affected by the parasitic plant[14]. The flowers are small and white having a perfect bell shape and a fleshy calyx attached directly to the stem nodes. *Cuscuta reflexa* makes the close contact to the host-xylem and phloem tissue via a specialized organ called haustoria[15]. Haustorium is a modified root which forms a physical contact between host and parasitic plant. It servesas channel for the movements of the solutes and carbohydrates. Haustoria release cell wall depredating enzymes which loosen the cell wall and able to penetrate to the stealer system of the host plants[16,17].

In agriculture, it is one of the most important weeds among the members of genus *Cuscuta*. It causes significant yield loss,

especially in alfalfa, sugar beet (*Beta vulgaris* L.) and other crop species. The devastating effect is caused by significant growth reduction of the host plants which ultimately leads into reduced biomass accumulation and poor seeds development of infested host plants[18]. Though *Cuscuta reflexa* harms crops including economically important crops, yet it possesses some medicinal properties. Each part of *Cuscuta reflexa* like stem, flowers, seeds accumulate many bioactive molecules which are antioxidant, antibacterial, anticancer in properties and can be used in many formulations to cure the various kind of disease.

Ethno medicinal importance of *Cuscuta reflexa*

Cuscuta reflexa is used for the treatment of various kinds of disorders like headache, muscle pain, jaundice, etc. in many tribal villages in India. The whole plant extract paste is used to get the relief from headache occurs during cold and rheumatism disorder. *Cuscuta reflexa* juice is also helpful in the treatment of blood-related disorders as well as the treatment of jaundice. Anthelmintic and carminative properties are associated with the seed of *Cuscuta reflexa*. The extracts obtained from seed are also used in bilious disorder. The extracts of *Cuscuta reflexa* also function as relaxant and spasmolytic[19].

Phytochemicals obtained from *Cuscuta reflexa*

Cuscuta reflexa contains a group of stems holoparasitic dicotyledonous angiosperms which affects many economically important crops. Physical connections via haustoria are formed by the parasitic plant to the stelar system of host plants. These connections serve as channel for the movement of photosynthetic solutes and water from host plant to the parasitic plant. The dependence of *Cuscuta reflexa* for the metabolites on their host leads to the differential accumulation of the phytomolecules. Chemical constituents predominantly reported in *Cuscuta reflexa* are cuscutin, cuscutalin, dulcitol, mannitol, sitosterol, carotenoids, flavonoids, alkaloids, di and tri-terpenes, polyphenols, reflexin, violaxanthin, lutein, lycopene, carotene, cerotic, linolenic, oleic, stearic, and palmitic acids, phytosterols, leuteolin and its glycosides, ambebelin, amino acids, lupeol etc. The chemical constituents mainly depend on the host plants. The table represents the major class of metabolites present and their nature of action (Table 1).

Table 1: Bioactive molecules present in *Cuscuta reflexa*

Phytochemical Component	Major biological activity
1. Alkaloids	Antitumor, Cancer preventive, Antioxidant
2. Terpenoids	Antibacterial, Antioxidant, Antitumor, Cancer preventive, Immunostimulant, Chemo preventive
3. Sterol	Antimicrobial, Anti arthritic, Antiasthma, Anti-inflammatory
4. Flavonoids	Antimicrobial, Anti-inflammatory, Antioxidant
5. Phenolic compounds	Analgesic, Anesthetic, Antioxidant, Antiseptic, Antibacterial, Antiviral Cancer
6. Resin glycosides	Antibacterial, Antioxidant

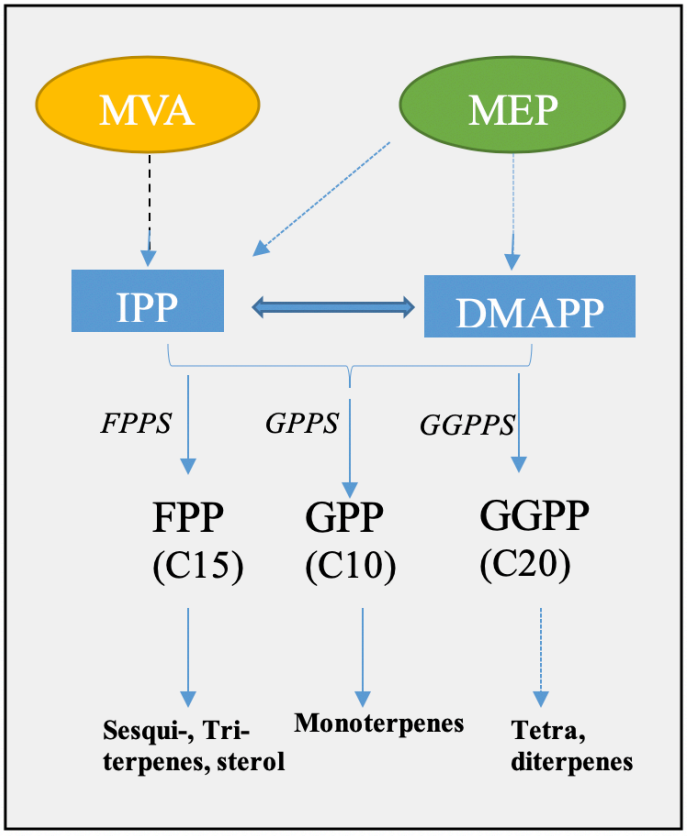

Figure 1: Simplified view of common secondary metabolites biosynthetic pathways in plant
Basic secondary metabolites pathways share by the all plant species, where dotted like represents the many enzymes are involved and single line present the one step reaction. Letters in italics represents the genes.

Pharmacological activities of *Cuscuta reflexa*

Cuscuta reflexa has a wide range of biological activity. Extract obtained from different solvent methods has antimicrobial, anti-cancer, anti-inflammatory, antioxidant and hepatoprotective activity etc.

Antioxidant activity

In vitro antioxidant activity of *Cuscuta reflexa* stems were investigated by estimating free radical scavenging activity *via* 1,1-diphenyl-2-picryl-hydrazyl (DPPH) method which is the easiest and commonly used method. Two compounds isolated from the *Cuscuta reflexa* extract significantly reduced the concentration of DPPH radical. Thus, it showed the extract possesses potent antioxidant activity[20]. The fraction collected by the ethyl acetate and ethanol showed higher antioxidant activity than other fractions[21].

Antimicrobial activity

Ethanolic extracts obtained from *Cuscuta reflexa* stem showed a broad range of antimicrobial activity. The extract was tested against both gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and gram negative (*Escherichia coli* and *Salmonella typhi*) bacteria in a dose dependent manner[22]. Bacteria were subjected to the gradient concentration from 200 to 500 microgram/ ML. maximum zone of inhibition was observed at 500 microgram/ ML concentration to all of the tasted bacteria except for *Salmonella typhi*. The results indicated that ethanolic extract of stem of the plant possessed antibacterial and cytotoxic properties due to the presence of several numbers of chemical compounds[23]. A new bioactive molecule 3', 4'-dimethoxy-1-phenyl-1a, 2-ethanediol was characterized recently by methanolic extraction followed by ethyl acetate extraction showed activity for both bacteria as well as fungi[24]. It has been reported that the ethanolic extract of *Cuscuta reflexa* showed more inhibitory effects on gram negative bacteria like *Escherichia coli*, *Pseudomonas aeruginosa* compared to fungal strains like *Penicillium citrinum*, *Aspergillus niger* using standard drug such as Penicillin[25]. Thus, different extraction methods have different range of microbial activity.

Anti-HIV activity

Cuscuta reflexa also shows activity against viral infection. The crude soluble extract obtained from the whole plant of *Cuscuta reflexa* showed anti-HIV activity, the flavones present in the extract might decipher this activity. The flavones bind to V3 loop and inhibit its interaction to CD4 or possibly directly act on the viral protease. This leads into the non-viral replication and ultimately leads to the viral degradation. This could be also dependent on the combinatory effects with other compounds of their different modes of action[26,27].

Antidiabetic effects

The crude extract of *Cuscuta reflexa* by methanol and aqueous has antidiabetic property in a dose dependent manner. When diabetic rat was infested with 400 mg/kg of methanol extract reduced the 61.90 % of glucose level after 8 hours of treatment. Whereas aqueous phase extract able to reduce only 55.39 %. This affect also associated with the increase in the overall body weight of diabetic rat. Overall methanol extract of *Cuscuta reflexa* has significant anti diabetic effects[28].

Diuretic activity

Diuretics are the drugs which can increase the urine flow *via* dilation of the urinal tract. *Cuscuta reflexa* plant extract of alcoholic and aqueous phase present the phytoconstituents like phenolics mainly flavonoids and tannins showed diuretic activity[29,30].

Anti-arthritic and nephroprotective activity

Anti-arthritic activity of *Cuscuta reflexa* extract was evaluated. Fraction collected from aqueous and methanol was used in *in-vivo* experiment where formaldehyde induced arthritis and turpentine oil-induced arthritis models. Methanol extract significantly reduced the edema in paw, in formaldehyde induced arthritis models as compared to the control experiment; whereas turpentine oil-induced arthritis models also showed the significant reduction of joint cavity swelling as compared to the control. This result shows that *Cuscuta reflexa* extract provides protection against arthritis. *Cuscuta reflexa* extract also possess nephrotoxicity[31].

Anti-inflammatory and anti-cancer activity

Alcoholic and aqueous extract of *Cuscuta reflexa* stem has anti-inflammatory activities. A fraction collected from aqueous extract was analyzed in *in-vitro* and anti-inflammatory activity was observed in murine macrophage cell line RAW264.7, using lipopolysaccharide (LPS) induced inflammatory reactions. The expression level of key genes like *COX-2* and *TNFα* was analyzed. The expression of these two genes induced significantly when cell was treated with LPS as compared to the control. Cell treated with the alcoholic extract of *Cuscuta reflexa* was able to reduce the expression level of these two important genes, which are playing crucial role in inflammation. These results indicate its efficacy in protecting the cells from acute inflammation[32]. Anti-inflammatory activities were observed in carrageenan induced paw edema model in rats, when *Cuscuta reflexa* extract was orally infested to the diseased rat[33]. The extract of *Cuscuta reflexa* was also tasted for the anti-cancer activities, the hepatocellular carcinoma cell line. Hep3B was used for anticancer assay. The cells treated with the *Cuscuta reflexa* extract significantly reduced the expression levels of survivin, which are necessary for a cancer cell to maintain its proliferative nature[32]. The reduced level of survivin leads into the apoptosis of cancerous cell[34,35].

CONCLUSION

Medicinal plants possess secondary metabolites. Due to the presence of these molecules, plants have curative properties. These secondary metabolites are classified as alkaloids, flavonoids, phenolic compounds, steroids, essential oils, etc. according to their chemical structures and properties. Now a day most of the drugs depend on plant sources or plant extracts. These extracts are used to cure various kinds of ailments. Studies conducted *in-vitro* and *in-vivo* models have provided evidences for various pharmacological activities and ethnomedicinal uses. This strongly indicates that *Cuscuta reflexa* is useful in different diseases like jaundice, muscle pain, coughs and problems associated with the urination. *Cuscuta reflexa* used in the Indian system of Ayurvedic and is a very rich source of many different kinds of secondary metabolites.

Future scope for the research

Cuscuta reflexa is a holoparasite to the stem its chemical contents are mainly depending on the host plant. Research work on *Cuscuta reflexa* has recently become popular because of its focus

on the identification of the bioactive molecules and its pharmacological activities. However very few reports are there on side effects or toxicity and their mechanism of action. Recent studies are also suggesting that *Cuscuta reflexa* transmit the signals of biotic and abiotic mobile molecules from one plants to the another plant which are physically separated but are attached via *Cuscuta reflexa*[36,37]. These researches open up with the new direction of research on *Cuscuta reflexa* as an indicator for various kinds of stresses. The future research will be mainly focusing on its toxicity effects and mechanism of action of the phytochemicals isolated from *Cuscuta reflexa*. Apart from these, it will focus on the identification of new compound which can be used as an indicator for the biotic or abiotic stress.

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