Review article

A review on phytochemical and pharmacological potential of genus Chelidonium

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A R T I C L E  I N F O

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A B S T R A C T

Many herbal remedies have so far been employed for the treatment of various ailments since the beginning of human civilization. Chelidonium is the smallest genus of family Papaveraceae, occurring in Europe and Asia. This review is intended to integrate traditional ethno-medical knowledge and modern scientific findings about Chelidonium majus in order to promote understanding of its therapeutic actions as well as its toxic potential. Through this review, the authors hope to attract the attention of natural product researchers throughout the world to focus on the unexplored potential of Chelidonium genus. An exhaustive literature survey revealed that alkaloids, flavonoids and phenolic acids constitute major classes of phytoconstituents of the genus. A few species of this genus have medicinal value, among these, C. majus Linn. (Papaveraceae) has been traditionally used in the treatment of skin diseases such as eczema, ringworm, oral infection, pains and nervous disorders. C. majus has also been included in homeopathic formulations which are in clinical use. Ukrain, a thiophosphate derivative of alkaloids from C. majus, exerts cytotoxic and cytostatic effects on tumor cells, simultaneously acting as an immune response modifier. C. majus seems to hold great potential for in-depth investigation for various biological activities, especially on central nervous system.

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1. Introduction

The use of plants as medicines or tonics goes back to prehistoric times and has attracted the interest of scientists for centuries. Medicinal herbs are the local heritage with global importance. Owing to the global trend towards improved “quality of life”, there is considerable evidence of an increase in demand for medicinal plants. India has a rich source of a wide variety of plants having medicinal value. These plants are widely used by all sections of society whether directly as folk remedies or indirectly as pharmaceutical preparations of modern medicine.

The present review emphasizes ethnopharmacology, morphology, phytoconstituents, pharmacological reports, clinical studies and toxicology of the prominent species of Chelidonium. Through this review, authors hope to attract the attention of natural product researchers throughout the world to focus on the unexplored potential of the Chelidonium species. This genus needs to be investigated systematically so that potential species can be exploited as therapeutic agents.

1.1. The genus Chelidonium

Chelidonium, the smallest genus of about 30 species of the family Papaveraceae, is distributed throughout Europe and Asia. The members of Chelidonium are herbaceous. Chelidonium majus commonly known as Greater Celandine, is widely distributed in Europe and Western Asia where it grows on hedge banks.
proven to be safe as components of veterinary and human phytopreparations.10

C. majus is used in various complementary and alternative medicine (CAM) systems, including homeopathy, mainly in combating diseases of the liver,11 stomach and various skin disorders.12

1.3. Morphology

C. majus is a perennial herbaceous plant growing wild in both Europe and America, recognized readily by its pinnate leaves, small peduncled yellow flowers and yellow opaque juice. Roots several headed, branched, reddish brown; stem 50 cm long, light green, hairy; leaves 15 cm long, thin, petiolate; flowers in small, long peduncled umbels with two sepals and four yellow petals, each 1 cm long (Fig. 1); fruit linear, capsule two valved and many seeded; seeds small, black and possess an elaissome which attracts ants to disperse the seeds.3 The fresh plant contains a saffron colored milky juice, and has an unpleasant odor and acrid taste. The flowers appear from May to July.3,13

1.4. Microscopic characteristics

The transverse section of the stem is circular, covered by a thin cuticle. The epidermal cells have very thick walls. One or two layers of thin-walled chlorenchymatous hypodermis partly transformed into collenchyma. Cortex consists of polygonal, very thick-walled cells (sclerenchyma). Very few thin-walled 5—10 cells long, uniseriate covering trichomes, are present along with few anomocytic cells (sclerenchyma). Very few thin-walled chlorenchymatous hypodermis partly transformed in collenchyma. There are multicellular, very few covering trichomes, uniseriate with 5—10 cells long, uni- seriate covering trichomes, are present along with few anomocytic stomata.

The petiole has stem-like structure. The chlorenchyma is almost entirely transformed in collenchyma. There are multilocular, very thick covering trichomes. Leaf epidermis has sinuous anticinal walls; very few covering trichomes, uniseriate with 5—10 thin-walled striated cells. Stomata anomocytic, exclusively on the lower epidermis. Mesophyll is differentiated into a layer of palisade and two layers of spongy parenchyma made up of thin-walled chlorenchyma. Midrib consists of 1—2 layers of collenchyma and thin-walled parenchymatous ground tissue. Calcium oxalate crystals and yellow-green fluorescent zones at Rf approximately 0.2; directly above this is the narrow yellow-green zone of cheler-thryrine, followed by the tailing yellow zone of sanguinarine. The pale white fluorescent zone of protopine is located in the same position as standard berberine.19

1.6. Physicochemical parameters

Table 1 shows the values of various physicochemical parameters.14,16,20

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign organic matter</td>
<td>NMT 1</td>
</tr>
<tr>
<td>Total ash</td>
<td>NMT 13</td>
</tr>
<tr>
<td>Acid-insoluble ash</td>
<td>NMT 2</td>
</tr>
<tr>
<td>Water soluble extractive</td>
<td>NLT 20</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>NMT 10</td>
</tr>
</tbody>
</table>

1.7. Phytoconstituents

Exhaustive survey of literature revealed that only three species of Chelidonium have been investigated phytochemically. Table 2 summarizes the phytoconstituents of different species of Chelidonium. Structures of some of the constituents reported from various Chelidonium species are shown in Fig. 2.

1.8. Pharmacological reports

The available literature reveals that amongst 30 species of Chelidonium, only one species, i.e., C. majus has been evaluated for its pharmacological activity. The plant exhibits multiple biological actions such as antiviral,14 antitumor,45 antibacterial/antifungal46 and anti-inflammatory effects.47 In the following part these actions such as antiviral,14 antitumor,45 antibacterial/antifungal46 and anti-inflammatory effects.47 In the following part these
activities have been described with regard to the crude extract, the single alkaloids and the other non-alkaloid components of the plant.

1.9. Antiviral effects

The effects of *C. majus* extracts against influenza virus have been studied in *vitro* and in *vivo*. Total alkaloids were active in *vitro*.
against influenza virus\textsuperscript{48} and encephalomyocarditis.\textsuperscript{49} In mice with influenza-virus-induced pneumonia, the total alkaloids were therapeutically effective when the injected dose of the virus was low.\textsuperscript{48} Alkaloid extracts showed antiviral activity against human adenoviruses type 5 and 12, as well as against herpes simplex virus.\textsuperscript{44,50} Antiviral properties of \textit{C. majus} whole plant extracts were observed on the DNA herpes virus and the RNA poliovirus. The inhibitory effect of alkaline extract was higher than alcoholic extract, and the alkaline extract was more efficient against the herpes virus and the poliovirus.\textsuperscript{51}

Alkaloids extracted in acidic pH show significant inhibitory effect on adenoviruses type 5 and 12 and herpes simplex virus type 1.\textsuperscript{44} Protoberberine and benzophenanthridine alkaloids inhibited reverse transcriptase (RT) activity of RNA tumor viruses.\textsuperscript{44,52–55}

1.10. Antitumor effects

Galenic preparations of \textit{C. majus} aerial parts have been used in the treatment of malignant diseases for centuries, and the alkaloids are usually regarded as the tumor-inhibitory principles. The alkaloids chelidonine and protopine from \textit{C. majus} extract were tested as potential tumor inhibitors in the treatment of sarcoma 180 and Ehrlich carcinoma. Chelidonine (50 \textmu g/kg body weight of mouse) administered over 7 days exerted an insignificant tumor inhibition: 25% for sarcoma and 22% for Ehrlich carcinoma, with a mild cytotoxicity still present. Protopine (350 \textmu g/kg) administered intraperitoneally in 7 days exerted only a mild tumor inhibition: 15% for sarcoma 180 and 26% for Ehrlich carcinoma. These findings indicated that chelidonine and protopine, although they exert certain antitumor activity, have no therapeutic value due to their high cytotoxicity at therapeutic doses.\textsuperscript{56} Chelidonine N-oxide, a chelidonine derivative, had a higher anticancer activity than chelidonine.\textsuperscript{57}

Sanguinarine and chelerythrine produce a dose dependent increase in DNA damage and cytotoxicity in both primary mouse spleen cells and L1210 cells.\textsuperscript{58}

1.11. Antimicrobial activity

Pseudoalcholates of sanguinarine and chelerythrine showed consistent antimicrobial activity.\textsuperscript{59} These derivatives have a greater intercellular penetration and are active (MIC = 6.25 \textmu g/ml) against: \textit{Staphylococcus aureus}, \textit{Escherichia coli}, \textit{Salmonella gallinarum}, \textit{Klebsiella pneumoniae}, \textit{Mycobacterium smegmatis}, \textit{Candida albicans}. Chelidonine, chelerythrine and homochelidonine inhibit the growth of Gram positive bacteria \textit{in vitro}.\textsuperscript{50}

Benzophenanthridine alkaloids are used for treating periodontal disease. Antibacterial products incorporated into toothpastes and mouth rinses containing an aqueous solution of sanguinarine chloride 0.3% showed an antiplaque effect.\textsuperscript{51} Sanguinarine and chelerythrine were effective in controlling the production of volatile sulfur compounds responsible for bad breath.\textsuperscript{62} Oriental drugs containing berberine and other compounds effective against dental caries have been added to dentifrices and are covered by a patent.\textsuperscript{63}

Berberine in concentrations of 10–25 \textmu g/ml inhibited the growth of different genera of fungi: \textit{Alternaria}, \textit{Aspergillus flavus}, \textit{Aspergillus fumigatus}, \textit{Candida albicans}, \textit{Curvularia}, \textit{Drechslera}, \textit{Fusarium}, \textit{Mucor}, \textit{Penicillium}, \textit{Rhizopus oryzae} and \textit{Scopulariopsis}.\textsuperscript{54} Chelerythrine and sanguinarine, have antifungal activity on some Trichophyton strains, \textit{Microsporum canis}, \textit{Epidermophyton floccosum} and \textit{A. fumigates}.\textsuperscript{55} Chelidonine N-oxide, a chelidonine derivative exhibits comparable antifungal activity against moulds and yeast.\textsuperscript{57}

1.12. Anti-inflammatory activity

Sanguinarine, chelerythrine and quaternary benzophenanthridine fraction were screened for their anti-inflammatory activity in assays involving carrageenan-induced rat paw edema. Sanguinarine showed higher anti-inflammatory activity than chelerythrine.\textsuperscript{47} Stylopine, isolated from the leaves of \textit{C. majus}, in a dose of 0.001–500 mg/kg of body weight, is used to treat diseases caused by excessive inflammatory reactions.\textsuperscript{56} Sanguinarine-HCl and chelerythrine-HCl exhibit a direct inactivating action on lytic activity of phages of T1017 and T2 types acting on \textit{E. coli}.\textsuperscript{67} Ethanol extract of \textit{C. majus} shows elastase activity inhibition effect, collagen synthesis promoting effect and skin wrinkle improving effect without causing any skin irritation.\textsuperscript{68}

1.13. Anti-asthmatic activity

Total alkaloids from \textit{C. majus} prolong the latent period of asthma induced by histamine and acetylcholine and lower the number of animals experiencing asthma convulsions. Total alkaloids from \textit{C. majus} have marked anti-asthmatic action.\textsuperscript{69}

1.14. Activity of Ukrain on central nervous system

The effects of the thiophosphoric acid alkaloid derivative Ukrain (UKR-222) on the central nervous system of mice and rats were studied. Intraperitoneal administration of Ukrain in doses of 8.5 and 19 mg/kg to mice depressed spontaneous motor activity, decreased body temperature and potentiated the action of hexobarbital. Ukrain (19 mg/kg) also produced analgesic action in the hot plate test. It had no protective effect against electroshock. In rats, i.p. administration of Ukrain in dose of 14 and 28 mg/kg potentiated the action of amphetamine and apomorphine but had no effect on catalepsy induced by haloperidol. The central action of Ukrain seems to involve the stimulation of the dopaminergic system and the inhibition of the serotoninergic system.\textsuperscript{64}
1.15. Effect of C. majus extracts on choleresis

The total ethanol extract, the phenol and the alkaloid fractions of C. majus herb were tested for their choleretic activity using the isolated perfused rat liver. The total extract induced choleresis: the bile flow was significantly increased and the amount of bile was more than doubled after 40 min when compared to the pretreatment value. The phenol and the alkaloid fraction caused a slight, but nonsignificant bile flow increase. The combination of both fractions caused an increase of about 20% over pretreatment value, however, not significant. Although the total extracts induced choleresis, it was not possible to assign this activity to either the alkaloid or the phenol fraction.70

1.16. Antihapatotoxic activity

An aqueous-ethanol extract of Herba Chelidonii, containing 41–45% of ethanol exerted significant hepatoprotective activity against carbon tetrachloride (CCl4) toxicity in rats treated with varying doses of the extract. Intragastric administration of 12.5, 62.5 and 125 mg/kg body weight of the extract twice weekly over 3 weeks resulted in a reduction in CCl4 induced hepatotoxicity. Increased plasma activities of the enzymes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and lactate dehydrogenase, as well as the increased bilirubin level, induced by CCl4, were significantly decreased by the extract.71 A protection of the liver glycogen phosphorylase a and glucose 6-phosphatase activities against the toxic effects of CCl4 is observed when the ethanol extract (0.01 ml/100 g, daily) is administered.72

1.17. Antispasmodic activity

Chelidonine exhibits spasmolytic activity with its main effect on inhibiting smooth muscle activity.73 Protopine shows smooth muscle relaxant effects on isolated ilea of guinea-pigs, rabbits and albino rats and a marked relaxation of intestine in situ of anaesthetized dogs.74 An aqueous-ethanol extract of the herb containing 0.81% total alkaloids, calculated as coptisine, as well as the individual compounds, caffeoylmalic acid and coptisine, were examined for their activity against acetylcholine-induced contractions in ileum isolated from rats. Acetylcholine-induced contractions were slightly reduced by the extract (12.7%; 2 mg/ml), and by coptisine (16.5%; 0.1 mg/ml).75 In another study, acetylcholine-induced contractions in isolated guinea-pig ileum were antagonized by the addition of protopine and allocryptopine (IC50 2.3 μM) to the bath media, whereas berberine potentiated the contractions.76

1.18. Clinical studies

In clinical trials, C. majus extracts showed a demonstrable reduction of the sensation of pain. The analgesia lasted for 4–48 h. The extracts produced an increase in the excretion of urine with retention of calcium and sodium chloride.77,78 Ukran, given i.v. in a dose of 10 mg every three days causes an increase in both T-cells and T-helper lymphocytes, a decrease in T-suppressor cells and normalization of the helper/suppressor (HIS) ratio. A significant improvement from the use of Ukran as an immunostimulant in cancer patients can be achieved.78 A prospective observational study involving 608 patients treated orally with an aqueous-ethanol extract of the crude drug (5–7 ml, mean daily dose 375–500 mg extract, corresponding to 9–12 mg of total alkaloids) has been reported. The outcomes were measured using the Physicians’ Global Assessment of Efficacy (4-point scale). After an average of 22 days of treatment, symptoms (dyspepsia or cramps in the upper gastrointestinal tract) were reduced in most patients and the outcome was assessed as good or very good in 87.4% of the patients.79

1.19. Toxicology

On the isolated frog heart, chelidonine in a dose exceeding 0.05 mg produced arrhythmia, heart block and diastolic stoppage.72 Oral ingestion of C. majus extract has been reported to produce hemolytic anemia. It coursed with intravascular hemolysis, renal failure, liver cytolysis and thrombocytopenia.80 Acute hepatitis is also reported along with the intake of C. majus.81–83 Intraperitoneal administration of 350 mg/kg body weight of methanol extract of the herb to mice for 7 days resulted in a 20% mortality rate. The median lethal intraperitoneal dose for chelidonine was 1300 mg/kg body weight in mice and 2000 mg/kg body weight in rats. Sublethal doses of chelidonine induced sedation, tremor and decreased body temperature.84

1.20. Adverse reactions

Excessive ingestion of the decoction of C. majus may cause nausea and other gastrointestinal symptoms.84 In rare cases, hepatic inflammation and an increase in liver enzyme activity and serum bilirubin have been reported, all of which are reversible following discontinuation of therapy.85 A case of contact dermatitis was described after external use of the aerial parts of the plant.86 A case of contact-derived allergic balanoposthitis and paraphimosis was observed after topical application of Herba Chelidonii juice.87

2. Conclusion

Survey of ethnopharmacologic records shows that such information is available only on C. majus. Three species of Chelidonium (Table 1) have been partially investigated for their phytoconstituents. A close scrutiny of literature on Chelidonium reveals that only one species (C. majus) has been investigated pharmacologically. Pharmacological studies infer that C. majus exhibits anti-inflammatory, hepatoprotective, antifungal, antiviral, cytotoxic, antibacterial and spasmyloytic properties. C. majus has been included in a number of herbal and homeopathic formulations which are in clinical use for the treatment of various ailments. Mother tincture of the plant is available in Indian market, and is frequently used for the treatment of CNS disorders. Keeping in view the ethnopharmacology, phytochemical and pharmacological reports, low toxicity and frequency of use in homeopathic formulations, C. majus seems to hold great potential for in-depth investigation for various biological activities.

Few preliminary pharmacological reports support medicinal potential of Chelidonium species. These species need to be investigated systematically with a view to establish their pharmacological activities and mode of actions.

Conflicts of interest

All authors have none to declare.

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