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Chelidonium majus – an Integrative Review: Traditional Knowledge versus Modern Findings

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Keywords
Chelidonium majus · Greater celandine · Medicinal plant · Phytotherapy · Chinese medicine · Integrative medicine

Summary
Chelidonium majus L. (family Papaveraceae), or greater celandine, is an important plant in western phytotherapy and in traditional Chinese medicine. Crude extracts of *C. majus* as well as purified compounds derived from it exhibit a broad spectrum of biological activities (anti-inflammatory, antimicrobial, antitumoral, analgesic, hepatoprotective) that support some of the traditional uses of *C. majus*. However, herbal medicine also claims that this plant has several important properties which have not yet been scientifically studied: *C. majus* is supposed to have diuretic, antitussive and eye-regenerative effects. On the other hand, *C. majus* also has scientifically proven effects, e.g. anti-osteoporotic activity and radioprotection, which are not mentioned in traditional sources. Moreover, recent controversy about the hepatoprotective versus hepatotoxic effects of *Chelidonium majus* has renewed the interest of the medical community in this plant. This review is intended to integrate traditional ethno-medical knowledge and modern scientific findings about *C. majus* in order to promote understanding of its therapeutic actions as well as its toxic potential.

Schlüsselwörter
Chelidonium majus · Großes Schöllkraut · Heilpflanze · Phytotherapie · Chinesische Medizin · Integrative Medizin

Zusammenfassung
Chelidonium majus L. (Familie der Papaveraceae), das große Schöllkraut, ist eine wichtige Pflanze in der westlichen Phytotherapie und in der traditionellen chinesischen Medizin. Sowohl Rohextrakte von *C. majus* als auch isolierte Einzelsubstanzen zeigen ein breites Spektrum an biologischen Aktivitäten (entzündungshemmende, antimikrobielle, antitumorale, analgetische, hepatoprotektive), die im Einklang mit einigen traditionellen Verwendungen von *C. majus* stehen. Dennoch betont die Kräutermedizin auch, dass diese Pflanze verschiedene Eigenschaften hat, die noch nicht wissenschaftlich untersucht worden sind, z.B. ihre diuretische, antitussive und augenregenerative Wirkung. Es gibt jedoch auch wissenschaftlich nachgewiesene Wirkungen, die in traditionellen Quellen nicht beschrieben sind, z.B. die Hemmung von Osteoporose oder den Schutz vor Strahlen. Darüber hinaus haben aktuelle Kontroversen über die hepatoprotektiven versus hepatotoxischen Effekte von *C. majus* das Interesse der Medizin an dieser Pflanze neu geweckt. Dieser Übersichtsartikel soll das ethnomedizinische, traditionelle Wissen über *C. majus* und moderne wissenschaftliche Erkenntnisse integrieren, um zu einem besseren Verständnis der therapeutischen Wirkungen und des toxischen Potenzials dieser Heilpflanze zu gelangen.

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Introduction

Chelidonium majus L. (family Papaveraceae) is a plant highly praised for its therapeutic potential in western phytotherapy and traditional Chinese medicine (TCM). Popular names of the plant are: greater celandine, swallow-wort, or bai-qu-cai in Chinese.

The plant contains, as major constituents, isoquinoline alkaloids (such as sanguinarine, chelidonine, chelerythrine, berberine, protopine and coptisine), flavonoids, and phenolic acids [1]. Both crude extracts of *C. majus* and purified compounds derived from it exhibit a wide variety of biological activities (anti-inflammatory, antimicrobial, immunomodulatory, antitumoral, choleretic, hepatoprotective, analgesic, etc.) which are in concordance with the traditional uses of *C. majus*.

In this article, the pharmacological properties of *C. majus* according to scientific data will be reviewed in view of traditional claims, in order to create a synthetic description of this medicinal plant. Therapeutic properties claimed by herbal medicine but not yet studied by scientists (e.g. diuretic activity, and beneficial effects in eye diseases) as well as biological activities revealed by scientific tools, but until now unknown to traditional medicine (e.g. radioprotective or anti-osteoporotic activity) will also be mentioned.

A literature search using PubMed and Highwire was conducted to collect data from studies on pharmacological effects of *C. majus*. All data collected were published in English or German and available up to March 2010. '*Chelidonium majus*' and 'great celandine' were used as search terms. A supplementary hand search of the references in the identified articles and of different traditional or modern medical books was performed.

Description of *Chelidonium majus*

Description of Chelidonium majus *in Western Phytotherapy*

C. majus belongs to the large family of bitter tonic herbs. The medicinal virtues attributed to it are those of powerful deobstruent (particularly efficacious in removal of obstructions of the liver), analgesic, aperient, diuretic, sudorific, expectorant, and purgative. It has traditionally been used in western phytotherapy to treat liver diseases, gastric ulcer, oral infections, pain, skin eruptions, and tuberculosis. Externally, the juice of the plant has long been known as a popular remedy to remove warts, to heal old and non-responsive skin ulcers, and to remove opacities of the cornea (mixed with water as an eye water) [2–5].

Description of Chelidonium majus *in Traditional Chinese Medicine*

C. majus or bai-qu-cai belongs to the class of heat-clearing plants, having a cooling nature. As it also has a drying effect, it is a good remedy for conditions associated with damp heat, which may be related to congested bile or yellow discharge, and hence associated with infections (note: in Chinese medicine, heat and infections go together). In traditional Chinese medicine *C. majus* is mainly used to treat blood stasis (a kind of blockage in blood circulation due to stagnation of qi), to relieve pain (abdominal pain, digestive ulcer pain, cramps after meals, menstrual pain, etc.), to promote diuresis in oedema, ascites, to treat jaundice, and to relieve cough. Some of these effects (e.g. the analgesic and hepatoprotective effects) have already been recognised by modern medicine and will be discussed further [6, 7]. *C. majus* has a bitter taste. According to Chinese medicine, bitter taste affects the heart. However, a direct effect of *C. majus* on cardiac tissue has not yet been confirmed in research studies. The sole possible indirect correlation is supported by the antiplatelet effect of sanguinarine and protopine [8, 9] which might be useful in cardiovascular diseases.

Pharmacological Activities of *Chelidonium majus*

Anti-Inflammatory Activity

Animal studies: C. majus methanol extract significantly suppressed the progression of collagen-induced arthritis in mice. This action was characterized by a decreased production of TNF-alpha, IL-6, Interferon(IFN)-gamma, B cells, gamma-delta T cells (in spleen) and an increased proportion of CD4+CD25+ regulatory T cells. The serum levels of IgG and IgM RA factors were decreased [10].

Hypothesis: The anti-inflammatory activity of *C. majus* could be related to its heat-clearing and blood stasis-removing actions as mentioned in traditional sources. The traditional use of *C. majus* for different types of inflammatory pain (e.g. menstrual pain) is also based, at least in part, on this pharmacological activity.

Antimicrobial Activity

C. majus is listed among one of the most active antimicrobial plants in a screening study by Kokoska et al. [11]. Crude extracts of and several alkaloids isolated from *C. majus* exhibited antibacterial, antiviral, and antifungal properties [11–24] (table 1).

Immunomodulatory Activity

In vitro studies: An interesting immunomodulatory potential was exhibited by a protein-bound polysaccharide extracted from *C. majus* (CM-Ala), which showed mitogenic activity on spleen cells, bone marrow cells, and increased the number of granulocyte macrophage-colony forming cells (GM-CFC) [25]. When *C. majus* extract was used in combination with recombinant IFN-gamma, there was a marked combined induction of NO and TNF-alpha production in mouse peritoneal macrophages [26].

Table 1. Antimicrobial activities exhibited by *C. majus* constituents and extracts

Chemical constituents or parts used	Microbes	References
Antibacterial activity		
Root extract	Bacillus cereus Staphylococcus aureus	11
Chelerythrine	Streptococcus mutans	13, 14
8-Hydroxydihydrosanguinarine 8-Hydroxydihydrochelerythrine Glycoprotein CML Lectin	Staphylococci methicillin-resistant Staphylococcus aureus (MRSA)	12, 15, 16
Glycoprotein CML Lectin	multiresistant enterococci	15, 16
Sanguinarine	gram-positive bacteria, particularly Bacillus anthracis and staphylococci 98% of the isolates from human dental plaque	17, 18
Antiviral activity		
A new substance isolated from *Chelidonium majus*	human immunodeficiency virus 1 (HIV-1)	23
The totality of *Chelidonium majus* alkaloids	herpesvirus, poxvirus, grippevirus	24
Antifungal activity		
Root extract and aerial part extract 8-Hydroxylated alkaloids (8-hydroxydihydrosanguinarine and 8-Hydroxydihydrochelerythtine)	Candida albicans Fusarium oxysporum Botrytis cinerea clinical drug-resistant yeast isolates	11, 19–22

Animal studies: C. majus extract (1.25 ml/kg in single dose) suppressed immune responses locally by decreasing epidermal Langerhans cells and contact hypersensitivity by UVA irradiation in mice [19].

Human clinical studies: A clinical study showed that *C. majus* tincture improved cellular and humoral immunity, nonspecific resistance and promoted a reduction in the number of recurrences in children with chronic tonsillitis [27].

Hypothesis: Damp and heat produce each other. According to TCM the centre of this damp-heat pathology primarily lies in the spleen and stomach, as the spleen is the organ of damp and the stomach is the sea of food and water [28]. Low immunity and repeated infections represent one of the manifestations of damp-heat. Immunomodulatory activity including the mitogenic activity on spleen cells, and also gastroprotective [29] effects might be related with the drying and heat-clearing actions of *C. majus* and its traditional use in conditions associated with damp-heat.

Gastroprotective and Anti-Ulcerogenic Activities

Animal studies: An extract of *C. majus* has demonstrated anti-ulcerogenic activity against indomethacin-induced gastric ulcers in rats as well as antisecretory and cytoprotective activities. The anti-ulcerogenic activity was associated with an increase in prostaglandin E2 release and a decrease in leukotrienes [29].

Choleretic Activity

In vitro studies: Stimulatory effects of *C. majus* extract, and of alkaloid and phenolic fractions from it, have been reported on bile acid-independent flow in isolated perfused rat liver. After 40 min, the amount of bile was more than twice the initial value and the bile acid concentration was reduced. This effect could not be assigned to one of the two isolated fractions [30].

Human clinical studies: Two studies have confirmed the choleretic effect of *C. majus* in subjects with liver diseases and healthy volunteers. A hydroethanolic extract containing 1.5% of total alkaloids calculated as chelidonine administered intragastrically increased bile flow [31, 32]. Three more studies, cited by ESCOP, have shown the capacity of *C. majus* to ameliorate the biliary related complaints (table 2) [33–36].

Hepatoprotective Activity

Animal studies: The ethanolic whole extract exerted marked hepatoprotection against carbon tetrachloride toxicity in two studies on rats, indicated by a reduction in the number of necrotic cells, a prevention of fibrotic changes, and decreased activities of transaminases and bilirubin [37, 38]. It was also efficient in combating p-dimethylaminoazobenzene-induced hepatocarcinogenesis in mice [39].

Hypothesis: Choleretic and hepatoprotective activities of *C. majus* might be related to a deobstruent action on liver as mentioned in western phytotherapy sources.

Table 2. Clinical studies on *C. majus'* capacity to ameliorate biliary complaints

Study type [reference]	Daily dosage	Ameliorated complaints
Double blind placebo controlled study, 60 patients [34]	700 mg of a hydroalcoholic extract 5.3–7.7:1, corresponding to 24 mg of total alkaloids, 6 weeks	epigastric complaints or cramps in the biliary system and/or upper gastrointestinal tract
Retrospective study, 206 patients, 6 months [35]	solid preparation containing 125 mg of a hydroalcoholic extract corresponding to 0.675 mg of chelidonine and/or liquid preparation 3 × 20 drops corresponding to 0.15 mg of chelidonine	complaints related to gall stones or cholecystectomy such as bloating, flatulence, diarrhoea or constipation, lasting abdominal pain, food intolerance
Multicentric prospective observational study, 608 patients [36]	375–500 mg of a hydroethanolic extract 5–7:1, corresponding to 9–12 mg of total alkaloids, 22 days	dyspeptic complaints or cramp-like pains in the upper gastrointestinal tract

Anticancer Activity

In vitro studies: Different alkaloids of *C. majus* have the following activities that might be responsible for its anticancer effect: (a) reduced telomerase activity by chelidonine [40]; (b) cancer cell death by apoptosis [40–42], and blister cell death [42]; (c) arrest of mitosis by inhibition [40]. Several studies suggest that Ukrain™ (an anticancer drug whose major components are *C. majus* alkaloids chelidonine, sanguinarine, chelerythrine, protopine, and allocryptine) [41] exerts multiple selective effects on cancer cells: (a) cytotoxic effects on cancer cells without negative effects on normal cells [43]; (b) radio-sensitising effects on cancer cells, but radio-protective effects on normal cells [44].

Animal studies: C. majus extract has exerted inhibitory activity on glandular stomach carcinogenesis in rats treated with N-methyl-N'-nitro-N nitrosoguanidine (MNNG) and hypertonic sodium chloride [45].

Human clinical studies: Some clinical studies suggest beneficial effects of Ukrain in the treatment of patients suffering from bladder, breast, pancreatic, rectal, colorectal cancer, or Kaposi's sarcoma with even less adverse reactions when compared with conventional antineoplastic drugs. However, independent rigorous clinical studies and larger sample sizes are required before positive recommendations can be issued [46–49].

Hypothesis: According to Chinese medicine, blood stasis, pathogenic heat, and static phlegm are the principal causes for most cases of cancer pathogenesis [50]. Blood stasis is assumed to produce an accumulation of heat. An accumulation of excessive fluids followed by stasis and heat thickens the dampness which becomes sticky and turns into phlegm. The anticancerous potential of *C. majus* according to Chinese medicine is due to its multiple activities: elimination of blood stasis (antithrombotic, anti-inflammatory effect) and clearing the pathogenic heat (anti-inflammatory effect), and prevention of an accumulation of body fluids.

Analgesic and Antispasmodic Activity

In vitro studies: The aqueous extract of *C. majus* suppressed glycine and gamma-aminobutyric acid (GABA) activated ion currents and elevated glutamate-activated ion currents in rat periaqueductal gray neurons, which represent a key structure of the descending pain control system [51, 52]. *C. majus* alkaloids also have an analgesic effect, similar to that of morphine, which may last 4–48 hours [6]. In addition, extracts of the herb *C. majus*, as well as isolated alkaloids, exhibited antispasmodic and relaxant effects on the abdominal and gastrointestinal muscles of animals, being especially efficient in treating abdominal pain [53, 54]

Human clinical studies: A dried extract of *Chelidonium* (5–10:1 / 131–104 mg, equivalent to 4 mg total alkaloids calculated as chelidonine) and *Curcuma* (12,5–25:1 / 45 mg) was given to 39 patients with dumpy or colicky abdominal pain in the right upper quadrant due to biliary dyskinesia, while placebos were given to 37 patients for 3 weeks, respectively. The reduction of pain was more rapid during the first treatment week in patients who received the extract than in patients who received placebos [55].

Hypothesis: In Neijing chapter 39, the Yellow Emperor says that when the continuous flow of qi and blood through the body within their channels is attacked by a cold pathogen, it stagnates and creates pain [28]. *C. majus'* capacity to modulate ion currents in neurons and to relax muscles might be an expression of the herb's potential to remove qi stasis.

Radioprotective Activity

An extract of *C. majus* (CM-Aia) was found to increase the number of bone marrow cells, spleen cells, GM-CFC, platelets and to favour survival at lethal doses in irradiated mice [56]. Also, Ukrain minimized the consequences of irradiation in the endocrine system of the trial animals (abnormal glucocorticoid reception) [57].

Anti-Osteoporotic Properties

Ukrain, when administered intraperitoneally to ovariectomized mature female rats, prevented the decrease of bone mineral density of the femur measured by energy x-ray absorptiometry densitometry [56], and increased the electron paramagnetic resonance (EPR) signal intensity of the femur [59]. These effects are most probably related to an increased production of estrogens [60].

Table 3. Hypothetical correspondences between traditionally recognised and scientifically proved activities of *Chelidonium majus*

Traditional data	References	Scientific data	References
I. Traditional therapeutic actions confirmed or correlated with scientific findings			
Deobstruent used in liver diseases and jaundice	2, 4, 5	hepatoprotective choleretic	22, 30, 31, 37–39, 55
Healing skin ulcers and gastric ulcers	2, 6	gastroprotective	29
Anodyne used for the treatment of various kinds of pains (e.g. tooth ache, abdominal pain, menstrual pain, etc.)	2, 6, 7	analgesic anti-inflammatory spasmolytic	9, 10, 25, 36, 51, 52–55
Heat clearing plant used in fevers and conditions associated with damp heat, such as infections, cancers	6, 7	antimicrobial immunomodulatory antioxidant	11–18, 20, 21, 24, 26, 27, 61, 62
Cleansing, alterative or eliminating toxins	2, 5, 6	antitumoral anticancer immunomodulatory antioxidant	64, 26, 40, 42, 43, 45–49 61, 62
Eliminate blood stasis	7	antithrombotic anti-inflammatory	8–10
Removal of warts	4, 5	immunomodulatory antiviral	19, 23, 24, 25–27
II. Traditional therapeutic actions not yet confirmed by scientific findings			
Drying effect, diuretic and useful in edema	2, 6	–	–
Expectorant, antitussive, useful in chronic bronchitis, pulmonary consumption, whooping cough	5, 6	–	–
Eye regenerative and removal of corneal opacities	3, 4	–	–
III. Scientific findings not specified in traditional sources or not correlated with traditional actions			
–	–	antiosteoporotic	58–50
–	–	radioprotective	44, 56, 57
–	–	neuroprotective potential (acetylcholinesterase inhibitor)	71

Antioxidant versus Pro-Oxidant Activity

Although alcoholic extract of *C. majus* showed strong antioxidant activity measured by different assays, e.g. 1,1-diphenyl-2-picrylhydrazyl radical scavenging assay or FRAP assay [61, 62], this does not depend on the alkaloid content of the drug or transition metal element content [61]. There is also an animal study that reported a slight but significant reduction of glutathione level and SOD activity in the liver, after oral administration of a massive dose of *C. majus* (1.5–3 g / kg / day) [63]. These results suggest that, in spite of its intrinsic antioxidant properties, *C. majus* might compromise the hepatic antioxidant protection in case of overdose.

Toxic Potential

C. majus exhibited several types of toxicity: cytotoxicity on tumoral cells, hepatotoxicity, and phototoxicity.

Cytotoxicity: Both *Chelidonium* extract and isolated alkaloids showed cytotoxic effects towards murine NK/Ly lymphoma cells, possessing DNA intercalating properties and DNA damaging capacity [64].

Hepatotoxicity: Several isolated cases of hepatotoxicity (e.g. acute cholestatic hepatitis) of *C. majus* have been reported [65–68]. All patients completely recovered after withdrawal of *Chelidonium*. Clinical recovery was rapid and the hepatic functions returned to normal within few months [65, 66]. In addition to these cases, some 40 cases of liver damage from *C. majus* have been reported to the German regulatory authorities [69]. Based on this data, *C. majus* has been banned from oral use in Germany and other European countries. There is also an animal study that found no hepatotoxicity at doses about 50–100 times higher than those generally used in humans [63]. An average daily oral dose of alkaloids (sanguinarine: chelerythrine 3:1) up to 5 mg / 1 kg animal body weight proved to be safe [88]. Based on a careful examination of the available evidence linking ingestion of *C. majus* with isolated cases of hepatotoxicity, the Australian Complementary Medicines Evaluation Commitee has recently recommended that all oral products containing *C. majus* have a warning label and be used under professional health-care supervision [70].

Phototoxicity: Plant extract-induced sunburn oedema and formation of sunburn cells in mice [19].

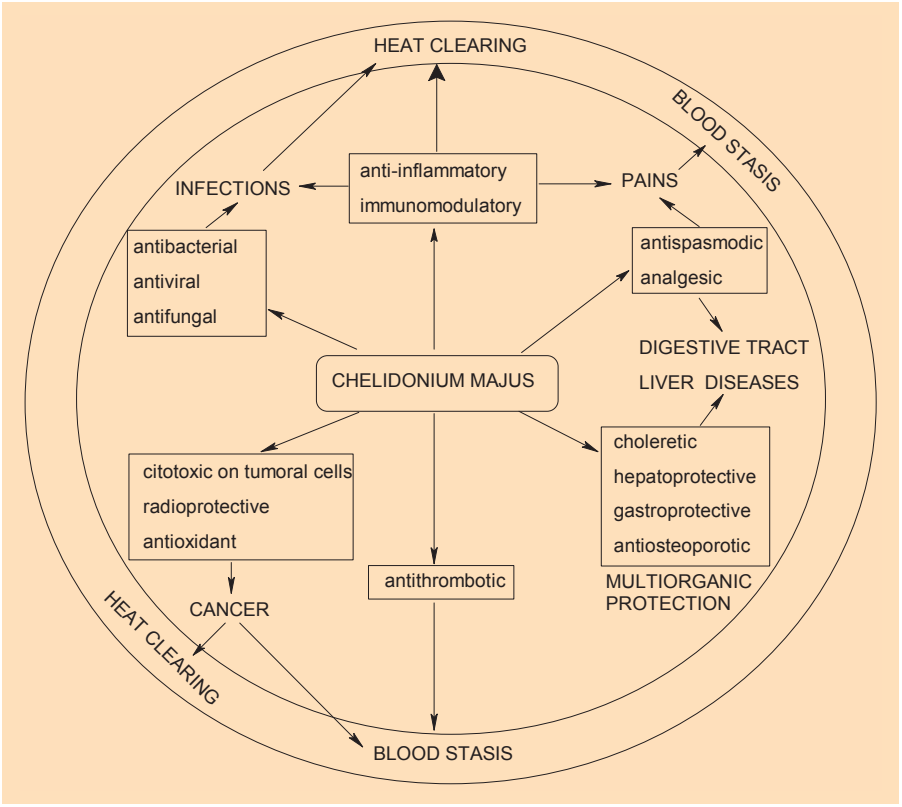

Fig. 1. Hypothesis on the pharmacological activities of *C. majus* in relation to Chinese indications. Elimination of blood stasis by *Chelidonium* might be correlated with anti-thrombotic, anti-inflammatory, and analgesic activities. Clearing the pathogenic heat might be correlated with anti-inflammatory, anti-infectious, anticancer, and antioxidant activities.

Conclusions

Despite major difficulties in explaining the traditional concepts in modern scientific language, we suggest further tests of several hypothetical equivalences concerning the therapeutic activities of *C. majus* (table 3).

The equivalence is not perfect or univocal: a single traditional term is usually explained by several modern terms. Modern terms also tend to be more specific than traditional terms (fig. 1).

We also have to take into consideration that the ancient non-quantifiable criteria for quality assessment (e.g. wet-dry, cold-hot) of herbal activities can not be replaced by simple biochemical or pharmacological measurements. Hence, to date an integration of TCM concepts into modern medicine is only possible to a limited degree, due to the fact that our previous scientific experience is mainly based on the *quantitative* evaluation of different biological parameters. On the other hand, the qualitative aspects, which are primordial in Chinese medicine, are almost completely ignored. The gap between these two systems will be filled when new scientific tools adequate for analyzing the *qualities* will be developed. Further fundamental studies and clinical trials are required in order to confirm the latent therapeutic potential of *C. majus* mentioned in traditional texts, and to find better ways of assessing the selective cytotoxic potential of this plant.

Disclosure Statement

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