European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 46-52

Hepatotoxicity induced by greater celandine (*Chelidonium majus* L.): a review of the literature

F. PANTANO[1], G. MANNOCCHI[1], E. MARINELLI[1], S. GENTILI[2], S. GRAZIANO[2], F.P. BUSARDÒ[1], N.M. DI LUCA[3]

[1]Unit of Forensic Toxicology (UoFT), Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Rome, Italy
[2]Drug Abuse and Doping Unit, Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Rome, Italy
[3]Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Rome, Italy

Flaminia Pantano and Giulio Mannocchi contributed equally to the manuscript

Abstract. – The available literature assessing Chelidonium majus L. (CM) hepatotoxicity potential, and its risk to benefit assessment has been reviewed in this paper. Identification of significant scientific literature was performed via the following research databases: Cochrane Central, Google Scholar, EMBASE, Medline, Science Direct, Scopus, Web of Science, using the following keywords: "Chelidonium majus", "greater celandine", "Hepatotoxicity", "Liver" "Injury", "Toxicity" individually investigated and then again in association. CM named also greater celandine, swallow-wort, or bai-qu-cai (Chinese), has been used for a long time in traditional Chinese medicine and phytotherapy. Its extracts have been claimed to display a wide variety of biological activities: antimicrobial, anti-inflammatory, spasmolytic, antineoplastic, hepatoprotective, and analgesic. Moreover, herbal medicine suggests this plant have numerous additional effects which have not yet been scientifically evaluated, such as antitussive, diuretic, and eye-regenerative. However, despite its claimed hepatoprotective effects, several hepatotoxicity cases have been reported to be probably or highly probably connected with CM exposure, after their evaluation through liver-targeted causality assessment methods. CM hepatotoxicity has been defined as a distinct form of herb-induced liver injury (HILI), due to an idiosyncratic reaction of the metabolic type. This evidence has to be considered in relationship with the absence of considerable benefits of CM therapy. Therefore, the risk to benefit ratio of the use of herbal products containing greater celandine can actually be considered as negative.

Key Words:
Chelidonium majus L, Greater celandine, Hepatotoxicity, Liver, Injury, Toxicity.

Introduction

Chelidonium majus L. (CM), also known as greater celandine, is a plant of the family Papaveraceae, which grows wild in part of Asia, Central and Southern Europe, in the Azores and North America[1,2]. It has been used for a long time in hepatobiliary disorders: gall bladder and digestive dysfunctions; dyspeptic complaints and spasms in phytotherapy and traditional medicine[3]. Currently, CM is widely marketed on the websites of natural products as a remedy against several medical complaints. The plant contains quaternary and tertiary benzo[c]phenanthridine alkaloids as major active components[4]. Recently, numerous hepatotoxicity reports have been suggested as linked with the use of herbal supplements containing CM[5,6]. However, the causal relationship between CM intake and the occurrence of liver damage has not yet been fully established[7]. Animal studies showed that the prolonged administration of high doses of CM to rats did not determine liver damage, leading the authors to suggest to exclude an intrinsic plant toxicity[8]. Hence, it has been hypothesized that the harmfulness could have been due to pharmacological interaction[9-12]. In this concern, the most severe reactions have been observed in subjects undergoing simultaneous treatment with CM and hormones (estrogens, thyroid hormones) and/or non-steroidal anti-inflammatory drugs (NSAIDs)[13]. The aim of this paper was to review the available literature assessing CM characteristics, risk to benefit ratio and its hepatotoxicity potential.

Corresponding Author: Francesco Paolo Busardò, MD, MSc, DipFMS; e-mail: fra.busardo@libero.it

Materials and Methods

The selection of appropriate scientific articles was performed through the following research engines: Cochrane Central, Google Scholar, EMBASE, Medline, Science Direct, Scopus, Web of Science, up to October 2016 using the following keywords: "*Chelidonium majus*", "greater celandine", "Hepatotoxicity", "Liver" "Injury", "Toxicity". The main keywords "*Chelidonium majus*" and "greater celandine" were searched individually and then in association with each of the others. The 244 and 57 sources initially found respectively with "*Chelidonium majus*" and "greater celandine", were screened to exclude papers not suitable for the purpose of the review and duplicate sources. Only 43 papers [1, 4, 7-8, 10, 13-50] (25 research articles, 8 case reports, 9 reviews and 1 book) were included in the results. Moreover, a hand search was performed through the references of the identified articles.

Results

CM Mechanism of Action

A huge number of studies have been developed to assess CM efficacy in a large number of conditions, as this plant has been claimed to produce a wide variety of pharmacological effects[1]. Medicinal properties of CM can be attributed to the isoquinoline alkaloids contained in the plant (root and aerial part). More than 27 components have been described and divided into three main groups: a) benzo[*c*]phenanthridines, among which there are two subgroups -quaternary (chelerythrine and sanguinarine) and -tertiary like chelidonine; b) protopine and derivatives such as allocryptopine; c) protoberberines (berberine, coptisine)[4]. The plant contains flavonoids and phenolic acids as well[14].

Anticancer activity of CM has been observed *in vitro* studies. The plant constituents determine cancer cell apoptosis and inhibition of mitosis[15-17]. Specifically, Ukrain, a semi-synthetic alkaloid derived from CM, is characterized by antitumor, antineoplastic and immunomodulatory properties, determining dose and time dependent cytotoxicity on cancer cell lines, among which those of breast cancer[18,19]. Moreover, these effects have been observed after the administration of the whole extract of CM[20]. Ukrain, showed therapeutic effects with low adverse reactions on various kinds of cancer (colorectal, breast, pancreatic, bladder) and on Kaposi's sarcoma, as highlighted by human clinical studies[21].

Also, CM action against inflammation has been studied in animal models, demonstrating that the methanol extract of this plant was able to inhibit the evolution of collagen-induced arthritis in mice, decreasing the synthesis of certain cytokines and modulating the amount of immune cells and immunoglobulins[22]. Kokoska and colleagues suggested that this herb could be one of the most active as an antimicrobial agent[23]. Choleretic activity has been studied on isolated perfused rat livers, on which alkaloid and phenolic fractions derived from CM and CM extract, determined a doubling of the amount of produced bile and a reduction of bile acid concentration, after 40 minutes[24]. The choleretic effect has also been studied in humans, through the administration of a hydroethanolic extract intragastrically in healthy patients and in subjects suffering from liver illness. Bile flow was found to be increased[25]. Liver protection has been studied on rats, evaluating the defense from the toxicity due to carbon tetrachloride, through the administration of a whole extract of CM in ethanol[26,27]. It has been shown that the previous treatment with CM was able to reduce the number of necrotic cells, the value of transaminases, bilirubin, and the fibrotic changes due to carbon tetrachloride exposure. Also, the hepatocarcinogenesis caused by p-dimethylaminoazobenzene was found to be antagonized by CM in mice[28]. Anti-ulcerogenic and gastroprotective effects of CM extract have been evaluated on gastric ulcers induced by indomethacin in rats. CM showed an action against the development of ulcers, enhancing the release of prostaglandin E2 and decreasing leukotrienes[29], and producing an antispasmodic and analgesic activity as well. The analgesic effect determined by its alkaloids was similar to that of morphine. The CM extracts produced a relaxing and spasmolytic action on the abdominal and gastrointestinal muscles in animal models, being able to reduce pain[30,32]. This effect was observed also in human clinical studies[33].

CM Hepatotoxicity

Animal Studies

Some studies on animal models have been developed in order to assess the defensive properties of CM constituents or their ability to enhance the toxicity of other molecules. The protective potential of chelidonine, the major active compo-

nent of *Chelidonium majus,* and of its poly lactide-co-glycolide (PLGA) poly incapsulated nanoform (nano-chelidonine), has been evaluated in the oxidative stress and hepatic toxicity induced by cadmium chloride ($CdCl_2$) in mice[34]. The study results showed that the exposure to $CdCl_2$ for 30 days (twice a week at the following dosage: 1.0 mg/kg body weight i.p.) caused oxidative stress through lipid peroxidation and accumulation of reactive oxygen species (ROS). The administration of nano-chelidonine after $CdCl_2$ exposure markedly diminished lipid peroxidation and oxidative stress and restored GSH (glutathione) levels. Therefore, nano-chelidonine was suggested as a protective agent, in mice, against cadmium toxicity. Also, the ability of CM to enhance the hepatic effects of acetaminophen at a sub-toxic dose was evaluated in rats[7]. If administered alone, CM did not modify liver parameters in male rats while in female animals a rise of fibrinogen levels was observed. No changes in hepatic histomorphology were noticed in both sexes. Liver alterations were observed after the administration of sub-toxic doses of acetaminophen, while the co-administration of CM did not enhance hepatotoxic effects. Additionally, the anti-tumor properties of CM and its modulation of enzyme activity in the liver have been studied administering a homeopathic extract (in micro doses Ch-30 and Ch-200) of CM to mice, during hepatocarcinogenesis induced by p-DAB (p-dimethylaminoazobenzene) compared to control groups[35]. All mice that were administered p-DAB developed liver tumors. Approximately the 40% of the animals in which p-DAB was administered in association with Chelidonium, did not develop liver tumors. Chelidonium homeopathic medicine showed an anti-tumor effect and an anti-genotoxic activity and favorably modulated the effects of certain enzyme markers. Moreover, the inhibition potency of CM alkaloids on several enzymes was tested in animal studies. Chelidonine, berberine, sanguinarine, and "Ukrain" (a semisynthetic drug derived from CM) displayed an irreversible inhibition of serotonin and tyramine oxidative deamination reaction, in rat livers mitochondrial monoamine oxidase (MAO)[36]. However, the same metabolic pathway was not blocked for the substrate benzylamine. This finding suggests that mainly oxidative deamination performed by MAO form A is blocked by CM alkaloids. Ukrain and chelidonine showed the strongest inhibition potency, while sanguinarine and berberine exhibited a weaker action[37]. Similarly, the inhibition potential of CM alkaloids, was studied in liver mitochondria of male albino mice[4]. The molecules showing greater inhibition strength in mitochondrial respiration were those containing a positive charge, for the presence in their structure of a quaternary nitrogen atom: chelerythrine, sanguinarine, berberine and coptisine. The uncharged CM constituents underwent more troubles in passing through the mitochondrial membrane. Berberine, was the most biologically active alkaloid tested, and for this reason, it should display the highest toxicity. Moreover, the effects of chelidonine, coptisine, chelerythrine, and sanguinarine were studied on oxidative phosphorylation and calcium accumulation in rat liver mitochondria[38]. Chelerythrine and sanguinarine determined a block of the absorption and the accumulation of calcium cations and repressed oxidative phosphorylation, while chelidonine did not influence the studied parameters. The effects observed on mitochondria are directly connected to DNA intercalating properties, as sanguinarine and chelerythrine are strong intercalators, while chelidonine is not. Finally, after oral administration of CM on Wistar rats for two or four weeks, at the following dosage: 1.5-3 g/(kg day) (this amount should be considered 50-100 times higher than that generally consumed by humans), no substantial change was noticed in animals, regarding to: body weight, food intake, enzyme activities and liver histomorphology. Nevertheless, a mild but significant reduction of GSH levels, as well as superoxide dismutase (SOD) activity was observed. Therefore, these mild alterations suggest particular caution in administering CM in conditions characterized by an impairment of liver function[8].

Human Hepatotoxicity Reports

The liver damage due to herbal remedies is also named: herb-induced liver injury (HILI). The latter represents a rare occurrence that follows the exposure in a small amount of susceptible individuals[39-41]. HILI features are comparable to those of drug-induced liver injury (DILI). While performing causality assessment, it is of primary importance to choose the proper evaluation method. Teschke and Danan stressed the concept that causality assessment in HILI suspected cases should be performed through the Council for International Organizations of Medical Sciences scale (CIOMS), also known as Roussel Uclaf Causality Assessment Method (RUCAM) which is an instrument validated for hepatotoxicity and specific for the liver[42].

Liver damage due to CM intake in humans has been mainly supported by case reports and

reviews that evaluated the cases reported in scientific papers and spontaneous signaled adverse reactions. The onset of haemolytic anaemia due to the oral ingestion of CM extract was firstly observed in 1990 and was characterized by intravascular haemolysis, thrombocytopenia, renal failure and liver cytolysis[43]. The patient underwent treatment with steroids, blood components, transfusion and with haemodialysis twice. The 12th-day complete resolution of the clinical features was observed. Similarly, a 42-year-old woman was admitted to the hospital because of the reappearance of acute hepatitis of uncertain origin[44]. Her past clinical history was characterized by alanine transaminase (ALT) elevation (concentration of 755 U/l), preceded by the intake of herbal remedies as an alternative medication, including common (or lesser) celandine. ALT maximum values during the hospitalization were 350 U/l. All other possible causes of hepatitis, such as viral infection, metabolic diseases, and autoimmune aetiology were excluded. Liver biopsy showed an acute necrotizing hepatitis. Treatment was performed mainly through the avoidance of re-exposure and liver enzymes returned normal. Concordantly, ten cases of acute hepatitis connected with the intake of CM preparations were noticed from 1997 until 1999 in Germany[13]. The evolution of liver impairment in these patients was mild to severe. In half of the cases, important cholestasis was detected, but was not followed by liver failure. Other potential sources of liver damage such as secondary biliary, alcoholic damage, viral hepatitis, hereditary and autoimmune conditions were excluded performing imaging procedures, laboratory tests and liver biopsies. These last were compatible with damage induced by drugs. The discontinuation of CM intake determined rapid recovery in patients and the level of liver enzymes returned normal in 2-6 months. Unintentional re-exposure determined recurrence of hepatitis in one patient, this fact, is the most appropriate criterion for HILI causality assessment[45]. In conclusion, a great percentage of unsolved cases of hepatitis could be related to CM. Moreover, the manifestation of jaundice related to acute hepatitis was observed in a 42-year-old woman, several weeks after the consumption a herbal remedy containing CM and curcuma root, which she took for a skin illness[46]. In accordance with the cases reported above, clinical conditions improved rapidly after the discontinuation of the herbal product and the hepatic functions were found to be normal within two months. Two cases of acute liver damage connected with the use of CM where also reported in 2003[47]. In both patients, other culprits of acute liver injury were excluded, in order to assess causality. A recurrence of cholestatic hepatitis after CM re-exposure occurred in one patient. The two patients recovered fully, but the authors highlight the fact that the authorization of CM administration should be reconsidered, as actually there is a lack of therapeutic benefits connected with this drug. Another case regards a 58-year-old man admitted with acute cholestatic hepatitis after the use of a CM preparation[48]. Histopathology showed a picture of drug-induced hepatitis however after discontinuation of the herbal product the patient recovered fully. A further case of liver damage was described in 2008, involving a woman admitted to the hospital for asthenia, nausea, anorexia and with deranged liver enzymes[49]. She was found to have used a *Lycopodium similiaplex* preparation (containing *Lycopodium serratum* and *Chelidonium majus*) for 8 weeks before the onset of symptoms. Liver biopsy was suggestive of a hypersensitivity reaction and concordantly with the other reports she fully recovered. Teschke et al[10] evaluated the connection between CM intake and hepatotoxicity in 21 published case reports, using a causality evaluation method specific for the liver, as a multitude of confounding variables might have misled causality. For this reason, all 21 cases were examined through the CIOMS scale, which considers: risk factors, the latency period, comedication and other alternative causes, the trend of ALT after drug withdrawal. The results showed a high probability of causality in two cases out of 21. Probable in six cases. Lower causality levels were found in the remaining cases in which the causality was excluded for three patients and recognized as possible in 10 cases. Regarding the 8 probable events, hepatotoxicity due to CM embodies an idiosyncratic reaction of the metabolic kind, while immunologic or mandatory hepatotoxic characteristics are missing. Therefore, an accurate search and identification of confounding variables should be performed while evaluating the cases, but there is striking evidence for HILI due to GC in the cases analyzed by the authors. Moreover, the same author evaluated 22 spontaneous cases from Germany attributing to 8 events, a highly probable or probable causality assessment, with a predominance for the female

gender[50]. All patients recovered. Taken together, the above-reported case reports actually support the hepatotoxic potential of CM preparations.

Conclusions

An abundant number of herbal remedies has been suggested to be linked with the risk of liver damage, this side effect, as well as others, must be clearly underlined, in the light of an increase of popularity of herbal preparations[51]. Moreover, the clinical effectiveness of these remedies is frequently only supposed and does not seem to counterbalance the potential risks. Although important evidence of hepatotoxicity in animal studies is still not well defined, CM extracts and constituents displayed alterations and inhibition of liver metabolism suggestive for hepatotoxic potential. Numerous reports have been published about hepatotoxicity cases following CM intake, and several of them have been reported to be connected with CM exposure with probability or high probability. Liver histology, when available, showed: liver cell necrosis (single or confluent), inflammation and more seldom cholestasis and fibrosis[52]. CM hepatotoxicity has been defined as a distinct form of HILI, due to an idiosyncratic reaction of the metabolic type. This fact has to be evaluated in relationship with the lack of substantial benefits due to the therapy with CM. For these reasons, currently, the risk to benefit ratio of the use of herbal products containing CM can be considered as negative, although the described hepatotoxicity has generally manifested a benign course with the recovery of the patients after discontinuation of the intake.

Authors' contributions

All the authors made substantial contributions to conception and design of the manuscript; GM, FP and SG performed the literature search and NML, FPB and SG revised it. All the authors have been involved in drafting the manuscript and revising it critically for important intellectual content and all of them have given final approval to the version to be published.

Acknowledgements

The authors thank Michele Sciotti for technical assistance in manuscript preparation.

Conflict of interest

The authors declare no conflicts of interest.

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