Chelidonium majus: Relevant safety aspects of a hepatotoxic plant, trawling the web

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LETTER TO THE EDITOR

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Chelidonium majus: Relevant safety aspects of a hepatotoxic plant, trawling the web

Chelidonium majus L. or greater celandine (Papaveraceae) is spread worldwide and represents a common plant of European folk medicine, whose use was also inspired by the theory of signatures. It is used both externally and internally either in combination or in monotherapy in the form of different preparations, and traditionally applied for the treatment of several diseases, particularly against bile and liver dysfunctions (Zielinska et al., 2018). Moreover, its fresh latex has been also applied for the treatment of dermatological disorders, including warts and corns, tinea infections, and eczema (HMPC, 2011). *C. majus* purified compounds have been associated to a broad spectrum of biological effects, such as anti-inflammatory, choleretic, antimicrobial, antiviral, analgesic, antispasmodic, and hepatoprotective; moreover, some studies have recently suggested anticancer properties (Orvos et al., 2015).

While relatively to its potential therapeutic uses there is still insufficient evidence of efficacy, several studies and case reports suggested hepatotoxicity related to *C. majus* use (Zielinska et al., 2018). Such events are particularly important because, as already mentioned, one of the main indications of *C. majus* relates to liver and biliary tract disorders due to its experimented cholagogue and hepatoprotective activities.

In 2011, the European Medicine Agency (EMA) has reported that a safe oral daily dose limit of *C. majus* should not exceed 2.5 mg in alkaloids (HMPC, 2011). Moreover, EMA has affirmed that evidences of *C. majus* clinical efficacy are still lacking and a well-established use indication cannot be supported. Traditional use for *C. majus* is hampered by a high number of spontaneously reported liver-biliary adverse drug reactions and the withdrawal of products in Member States due to safety concerns. Therefore, the benefit–risk assessment of oral use of *C. majus* must be considered negative (HMPC, 2011). In this context, we have conducted a Web search aimed to highlight misleading information on *C. majus* safety also accomplishing with our mission of e-Phytovigilance (herbal pharmacovigilance in Internet; [Maggini et al., 2013]).

The present study is part of the activities carried out from the Research and Innovation Center in Phytotherapy and Integrated Medicine (CERFIT) of the Careggi University Hospital (Florence, Italy) responsible for the phytovigilance of Tuscany Region (Italy). In particular, online phytovigilance (e-Phytovigilance) borns to elaborate and apply strategies aimed to reduce the onset of adverse effects, also serious, to herbal preparations recommended on the web.

Two of main sites for selling online, Amazon and eBay, were screened to find out the web pages available as of April 2019 that sold products containing *Chelidonium majus* L. The research was alternatively conducted with one of the three terms "Chelidonium," "Chelidonia," "Celidonia." We took into consideration all the pages published in English and Italian. Two investigators (N. L. and G. C.) independently reviewed the contents and selected the relevant web pages. Any disagreements were resolved through discussion and consensus with two other independent reviewers (E. G. and F. S.). Web search engine Google was also used to combine the three terms by using the Boolean operators "OR."

Eight years after the publication of EMA report (HMPC, 2011), we conducted a web search to identify the web pages recommending the use of *C. majus* and to analyze the information reported in these websites. The search in Amazon and eBay produced more than 700 records (Table S1). After excluding the nonrelevant pages (selling online of seeds, plants, or products only for external use), the remaining sites (n = 27) were listed in Table S2 with (1) *C. majus* claimed therapeutic properties, (2) the proposed use, (3) recommended dosages, (4) information concerning contraindications, warnings, precautions, and safety. Product information was summarized in Table 1. Most websites claimed *C. majus* therapeutic properties in a wide range of clinical conditions and recommended its internal use (n = 20), also for liver and gallbladder disease (n = 7). In some cases, this plant could be bought without any information on its consumption-related risks and with suggestion to its homemade preparation. Only in few cases, safety information was clearly described in a dedicated paragraph along with the recommendations relative to the product use during pregnancy and/or breastfeeding (n = 10) and to the need to consult a doctor (n = 10) while warning about children (n = 3) use and drug interaction (n = 6) were almost completely lacking. Finally, only one site accounted for the potential hepatotoxic effects of *C. majus* treatment.

Google search produced more than two million results, and several representative (n = 39) examples were reported in Table S3. Interestingly, preliminary search results (see Table 1) showed information more exhaustive than ones found in the two selling sites. In particular, warnings for children and hepatotoxicity were reported in nine websites, and 15 sites stated to ask a doctor before starting *C. majus* administration. However, most websites documented the internal use (n = 36) for liver disease (n = 30), and these were not only general sites but also cooking and herbalist websites. Information concerning

TABLE 1 Main information reported in the websites selling/describing products containing *Chelidonium majus* L

		Indication			Warnings							
	Website nation	None	Internal use	For liver	General	Pregnancy	Breastfeeding	Children	Drug interaction	Hepatotoxicity	Regulatory	Medical control
Amazon												
1	Italy				x							
2	Italy		x	x								
3	Italy	x	x									
4	Italy	x										
5	Hawaii		x		x	x	x	x	x		x	x
6	Ukraine	x	x									
7	USA	x	x		x	x	x		x		x	x
8	England	x									x	
9	USA		x								x	
10	USA		x		x	x	x			x	x	x
11	Italy											
eBay												
12	Italy	x										
13	Italy											
14	Israeli		x	x								
15	USA	x	x		x	x						x
16	USA		x	x	x	x	x		x		x	x
17	Poland	x	x									
18	Romania		x	x							x	
19	USA		x	x	x	x	x				x	x
20	Bulgaria	x			x							
21	Czech Republic		x	x								
22	Portugal		x	x								
23	UK	x	x		x	x		x	x			x
24	Russia		x									
25	USA	x	x		x	x	x	x	x		x	x
26	USA	x	x		x	x	x		x		x	x
27	USA		x		x	x	x					x
Google												
28	Italy		x	x	x							x
29	Italy		x	x	x	x		x		x		x
30	Italy		x	x	x						x	x
31	Italy		x	x	x	x		x				x
32	Italy		x	x	x	x		x		x		x
33	Italy		x	x	x							
34	Italy		x		x				x			x
35	Italy		x	x								
36	Italy		x	x	x							
37	Italy		x	x	x	x		x		x		x
38	Italy		x	x	x							x
39	Italy		x	x	x							

(Continues)

TABLE 1 (Continued)

		Indication			Warnings							
	Website nation	None	Internal use	For liver	General	Pregnancy	Breastfeeding	Children	Drug interaction	Hepatotoxicity	Regulatory	Medical control
40	Italy		x	x	x	x	x	x	x	x		x
41	Italy		x	x								
42	Italy		x	x	x							
43	Italy		x	x	x							
44	Italy		x	x								
45	Italy		x									
46	Italy				x							
47	Italy		x	x	x	x	x		x	x		
48	Italy		x		x							x
49	Italy		x	x								
50	Italy		x	x								
51	Italy		x	x	x							x
52	Italy		x	x								
53	Italy		x	x	x	x		x	x			x
54	Italy		x		x	x	x		x	x		
55	Germany		x	x	x							x
56	Switzerland		x	x								
57	Italy		x	x	x			x				x
58	England		x	x	x	x	x	x		x		
59	England	x	x		x	x	x		x			x
60	Spain		x		x	x						
61	England		x	x								
62	England		x	x	x	x	x			x		
63	England		x	x	x							
64	England		x	x	x	x	x	x		x		
Homeopathic products												
65	Italy	x	x									
66	Italy	x	x									

interactions with other prescribed drugs were lacking in most of the websites (mainly related to sedatives) while *C. majus* hepatotoxicity was reported in nine websites. Despite discouraging its recreational use, one website described *C. majus* use among "psychonauts," generally consuming high dosages of plants for a harmful use. Moreover, we chose not to report web pages on homeopathic products, but only two (65 and 66) representative sites (see Table S3) claiming their products "as homeopathic," while really, they were mother tinctures (hydro-alcoholic extracts not diluted according to the principles of homeopathy). It is important to emphasize that mother tinctures are improperly termed "homeopathic products" because they are not diluted and can be a paradox. Unknowingly, patients and doctors could be misled because they are homeopathic products only from the regulatory point of view, not substantial. And therefore, they should be called "phytotherapeutic" or "herbal" but not "homeopathic" products. In fact, in addition to alcohol, they contain the active ingredients present in the fresh plant.

A brief statement concerning the status of herbal/diet supplement (i.e., product not evaluated by the FDA and not intended to diagnose, treat, cure, or prevent any disease) was present in 11 websites (10 out of 11 were selling sites).

Results from the present study were alarming with the *C. majus* therapeutic properties claimed in almost all websites and its potential hepatotoxicity reported only in very few cases. In fact, the incidence of liver adverse events following *C. majus* use has been recently reviewed by Pantano and colleagues (2017). In their study, authors affirmed that, despite its claimed hepatoprotective properties, several hepatotoxicity cases have been reported to be probably or highly probably connected with *C. majus* exposure in general population. *C. majus* hepatotoxicity has been defined as a distinct form of herb-induced liver

TABLE 2 Regulation about *Chelidonium majus* products on the market in the European Member States (this table has been processed with the data of the EMA report (HMPC, 2011)

Regulatory status	No. of countries	European country
Oral use authorized	7	Austria, Bulgaria, Lithuania, Czech Republic, Estonia, Germany, Slovenia
Only external use authorized	4	Belgium, Hungary, Spain, Norway
Not authorized	7	Denmark, Iceland, Malta, The Netherlands, Slovak Republic, Sweden, United Kingdom
Not authorized in food supplements	1	Italy
No regulation	10	Cyprus, Finland, France, Greece, Latvia, Liechtenstein, Luxemburg, Poland, Portugal, Romania

injury (HILI), due to an idiosyncratic reaction of the metabolic type. These evidences have to be considered in relationship with the absence of considerable benefits of *C. majus* therapy. Therefore, the risk to benefit ratio of the use of herbal products containing greater celandine can actually be considered as negative. In humans, numerous reports have been reported in the last decades. The main clinical presentation of patients with HILI related to *C. majus* exposure included cholestasis and mild to severe liver impairments with quite well documented causality in most cases. To date, over 50 such cases have been recorded from Europe, mostly from Germany (Crijns, de Smet, van den Heuvel, Schot, & Haagsma, 2002; Hardeman, Van Overbeke, Ilegems, & Ferrante, 2008; Stickel et al., 2003; and reference inside). In Italy, the study by Moro and colleagues (2009) points out the concern about the safety of oral use of *C. majus*. Authors remind that plants used in traditional medicine are not necessarily harmless and that customers and prescribers should be aware of this, especially when an herbal drug is used with therapeutic purposes in the absence of reliable studies of clinical efficacy and benefit–risk assessment.

In this complex scenario, it is important to take into consideration that, to date, no specific active compound has been already directly related to the toxicity of *C. majus*. On the contrary, it has been suggested that drug interactions rather than direct toxicity are responsible for reported cases. Also, individual hypersensitivity or allergy has always to be considered (HMPC, 2011).

However, the systemic and uncontrolled therapeutic use of herbal preparations should be discouraged, while pharmacovigilance and phytovigilance measures should be implemented to recognize, to report, and to prevent possible complications in the general population.

Special precautions are also necessary, especially during pregnancy and lactation, people suffering from liver diseases or taking liver-damaging drugs, during polypharmacy and in patients affected by chronic diseases (Moro et al., 2009).

After all, due to the weakness of the evidence and the risks related to its hepatotoxicity, the oral use of *C. majus* L. is authorized only in seven out of 29 European countries; in 10, it is not regulated at all, and in most of them, it is authorized for external use only (Table 2). This is an absurdly different law, and, for us, the most important and binding thing is a uniform regulation. In the United States, *C. majus* is "not approved by the FDA."

In this framework, e-Phytovigilance acquires a central role in herbal pharmacovigilance. In fact, the Internet represents a large market where toxic natural products and misleading information can reach everyone (Maggini, Menniti-Ippolito, & Firenzuoli, 2018). Without a proper cultural background, patients' and customers' health could be threatened. Our results represent an attempt to comply with the obligation to implement the e-Phytovigilance, but European countries should officially establish an observatory to supervise the online information of natural products.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

Keywords

adverse effect, *Chelidonium majus* L, e-Phytovigilance, hepatotoxicity, medicinal plants

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.