Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case

Received: 2 March 2020 | Revised: 23 June 2020 | Accepted: 24 June 2020

DOI: 10.1111/bcp.14460

SYSTEMATIC REVIEW AND META-ANALYSIS

Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports

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Aims: Several cases of acute non-infectious cholestatic hepatitis recently appeared in Italy following consumption of *Curcuma longa*-containing dietary supplements. The aim of this research was to describe the Tuscan (Italy) cases of acute hepatitis and to compare them with similar cases of hepatotoxicity published in the literature by performing a systematic review.

Methods: Records of Tuscan cases of acute hepatitis were obtained from the Italian Phytovigilance system. Each spontaneous report was analysed in order to collect all relevant clinical information of patients and information concerning the *Curcuma longa*-containing dietary supplement. Moreover, both the RUCAM and WHO-UMC systems were used to evaluate the causal relationship between the use of dietary supplement and acute hepatitis. A systematic literature review was performed in MEDLINE and Embase and all case-reports and case-series published in English were included.

Results: Seven cases of acute hepatitis occurring in Tuscany up to September 2019 are described. In all cases, hepatotoxicity was associated with *Curcuma longa* formulations with high bioavailability and high dosage of curcumin/curcuminoids. The causal relationship was also supported by the *positive dechallenge* observed in most cases. In the 23 cases identified through the systematic review, the majority of patients were concomitantly exposed to at least one other medication and 16 of them experienced a *positive dechallenge*.

Conclusions: Within the frame of poorly controlled and regulated products, such as dietary supplements, the evaluation of Italian cases of *Curcuma longa*-induced acute hepatitis and the systematic review of literature confirmed the association between *Curcuma longa* and liver injury.

KEYWORDS

case report, *Curcuma longa*, dietary supplement, herb-induced liver injury, systematic review, turmeric

Niccolò Lombardi and Giada Crescioli are co-first authors. Alfredo Vannacci is the Principal Investigator.

1 | INTRODUCTION

Turmeric (*Curcuma longa* L from Zingiberaceae family, CL) has been widely used as a spice in foods and for therapeutic applications in dietary supplements (DS).[1] Nowadays, CL is one of the most popular DS worldwide, with exponentially increasing sales reaching US $69 million in the United States only in 2016.[2] Curcumin, a polyphenolic substance, is the major CL constituent and it comes from the rhizome of the plant; it is known as a generally recognized safe compound.[1]

In general, CL is considered nontoxic for humans, especially in oral administration. Several trials on humans have not shown toxic effects,[3–19] and curcumin is reported to be safe at the dose of 6 g/day orally for 4–7 weeks.[11] However, some adverse events (AEs) such as gastrointestinal disturbances have been reported during CL-containing DS administration.[17] Moreover, oral bioavailable formulations of curcumin were safe for humans at the dose of 500 mg twice a day for 30 days.[7] Although the US National Center for Complementary and Integrative Health has considered CL to be safe,[20] there are still few clinical and observational studies evaluating its safety, thus more evidence is needed. However, we must point out that the European Food Safety Authority (EFSA) authorizes a 3 mg/day dose of curcumin as additive.[21]

In recent years, some reports of AEs related to the use of CL-containing DS have been published,[22,23] raising the issue of CL safety, in particular with reference to herb-induced liver injury (HILI). Recently, several cases of acute non-infectious cholestatic hepatitis cases, associated with the consumption of CL-containing DS, have been reported in Italy.[24]

We have collected and describe here seven cases of acute liver injury in subjects taking CL-containing DS. These cases have been observed in Tuscany (Italy) and recovered through the Italian Phytovigilance database. Moreover, we have performed a systematic review of case reports published in the scientific literature, describing their clinical characteristics.

What is already known about this subject

- Turmeric is considered nontoxic for humans, especially in oral administration.
- Several trials on humans have not shown toxic effects.
- Several cases of acute non-infectious hepatitis, associated with the consumption of turmeric-containing dietary supplements have been reported recently in Italy, particularly in Tuscany.

What this study adds

- Hepatotoxicity observed in our cases was associated with turmeric formulations with high bioavailability and high dosage of curcumin/curcuminoids.
- In the 23 cases identified through the systematic review, the majority of patients were concomitantly exposed to at least one other medication.
- Liver injury associated with *Curcuma longa* intake is a concrete risk, needing further attention by clinicians.

2 | METHODS

2.1 | Case-series

We retrieved spontaneous reports of suspected AE of acute hepatotoxicity related to CL-containing DS. Cases were obtained from the Italian Phytovigilance system, set up in 2002 and coordinated by the Italian National Institute of Health.[25–27] Although for the same period several hepatic events related to CL-containing DS were reported all over Italy, we analysed and included only AE reports from Tuscany based on a specific decision of the Italian National Institute of Health. The Institute allowed us, as a regional centre of pharmacovigilance and phytovigilance, to describe only events collected in our region.

Two different methods were used to evaluate the causality assessment between the suspected CL-containing DS and the related hepatic AE (Table 1). The first was the RUCAM (Roussel Uclaf Causality Assessment Method),[28,29] a well-established tool used to quantitatively assess causality in cases of HILI. RUCAM is a structured, standardized, validated and hepatotoxicity-specific diagnostic approach that attributes scores to individual key items, providing final quantitative gradings of causality for each suspect herb in a case report. The second tool applied was the WHO-UMC system for causality assessment.[30]

2.2 | Systematic review

Data for the systematic review were obtained through a search strategy that included three domains: one related to CL, one related to hepatotoxicity, and one related to paper language. Electronic searches were performed in the MEDLINE and Embase databases. The MEDLINE search strategy is reported below:

1. (curcumin*[tiab] OR turmeric*[tiab] OR turmeric yellow[tiab] OR *Curcuma longa*[tiab] OR "Curcuma"[Mesh] OR "turmeric extract"[Supplementary Concept] OR "Curcumin"[Mesh])
2. (liver injury[tiab] OR HILI[tiab] OR hepatopathy[tiab] OR hepatic[tiab] OR "Chemical and Drug Induced Liver Injury, Chronic"[Mesh] OR "Chemical and Drug Induced Liver Injury"[Mesh] OR "Acute-On-Chronic Liver Failure"[Mesh] OR "Liver Failure, Acute"[Mesh] OR "Liver Failure"[Mesh] OR "Liver Diseases"[Mesh] OR "Hepatic Insufficiency"[Mesh])

TABLE 1 Tuscany cases: serum and liver indices of Tuscany case series at the time of emergency department admission

	Age/gender	ALP (50–136 IU/L)	ALT (0–35 IU/L)	AST (0–40 IU/L)	GGT (5–85 IU/L)	DB (0–0.25 mg/dL)	TB (0.2–1 mg/dL)	Daily dose	Time to onset	Positive dechallenge	RUCAM	WHO-UMC
Case 1	55 years/F	–	2,800	900	–	–	8.0	1,470 mg	2 months	Yes	Probable	Probable
Case 2	62 years/F	–	1,578	2,499	–	15.0	25.0	1812,5 mg[a]	8 months	Yes	Possible	Probable
Case 3	59 years/M	–	3,303	7,883	298	–	–	280 mg	NR	Yes	Unlikely	Unassessable
Case 4	45 years/F	274	1,846	1,277	504	–	6.0	1,000 mg	2 months	NA	Possible	Probable
Case 5	68 years/F	–	257	173	141	–	–	600 mg	2 months	Yes	Probable	Possible
Case 6	56 years/F	–	3,087	1,512	124	–	11.1	1,000 mg	1 months	NA	Possible	Possible
Case 7	61 years/F	–	2,360	1,336	–	3.9	–	250 mg	2 weeks	Yes	Probable	Probable

[a]Mean value.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; F, female; GGT, gamma glutamyltransferase; IU, international unit; M, male; NA, not applicable; TB, total bilirubin.

3. (french[lang] OR spanish[lang] OR german[lang] OR chinese[lang] OR hindi[lang] OR arabic[lang] OR italian[lang] OR turkish[lang] OR swedish[lang] OR danish[lang])
4. 1 AND 2
5. 4 NOT 3

Records were retrieved on the same day from all sources. Two investigators independently selected the studies, reviewed the main reports and supplementary material, and extracted all relevant information for the included studies. Moreover they assessed the quality of the included case series/reports according to the tool proposed by Murad et al.[31] An overall judgement of methodological quality was made based on the extracted information, and studies were given a rating of low, moderate or high (Supporting Information Table S3). Discrepancies were resolved through discussion or in consultation with a third reviewer. We included only case reports and case series, carried out in humans and published in English in scientific journals between January 2000 and June 23, 2020. In case of doubt or missing information concerning case reports and case series retrieved by the literature review, we contacted the authors of the paper in order to complete the description of cases. This systematic review was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[32]

3 | RESULTS

3.1 | Tuscany cases

Thirty-seven acute hepatic events, out of a total of 73 spontaneous reports related to CL, occurred in Italy up to September 2019. We describe here the seven cases (six female) reported by healthcare professionals operating in Tuscany (Italy) between December 2018 and July 2019 (Table 1). Patients' age ranged between 45 and 68 years. The daily dose of CL varied between 250 and 1,812.5 mg for an exposure period between 2 weeks and 8 months. Positive dechallenge was observed for the majority of patients. Applying the RUCAM score (Table S1), three cases were judged as "probably", three as "possibly" and only one case as "unlikely" related to CL, while applying the WHO-UMC tool, five cases were judged as "probable", one case as "possible" and one case as "unassessable".

3.1.1 | Case 1

A 55-year-old Caucasian female was hospitalized and diagnosed with hepatitis after an in-depth clinical investigation performed in the emergency department (ED), which revealed altered hepatic parameters (Table 1): alanine aminotransferase (ALT) 2,800 IU/L (range: 0–35 IU/L), aspartate aminotransferase (AST) 900 IU/L (range: 0–40 IU/L) and total bilirubin (TB) 8 mg/dL (range: 0.2–1 mg/dL). The patient was a healthy subject and her anamnesis did not report any history of hepatic disorders or any other relevant concomitant condition. The analyses performed during hospitalization were negative for

hepatitis viruses (types A, B and C), cytomegalovirus (CMV), Epstein–Barr (EBV) and autoantibodies, as well as Wilson's disease.

In the ED, the patient reported that she had been taking 3-per-day tablets of a liver detoxifier for a period of 2 months. As reported on the product label, one tablet of the suspected product contained: *Curcuma longa* L. rhizomes dry extract (400 mg) and turmeric rhizomes powder (90 mg) (brand name TURMECUR®, 60 tablets, 500 mg each). The patient denied using any concomitant medication or other products. The patient also stated that she had not been exposed to substances known to be toxic to the liver, such as alcohol.

Intake of the suspected product was suspended at the time of hospital admission and hepatic parameters reverted to normal values over the subsequent 20 days (positive dechallenge). The AE resolved completely without the need for any specific therapy.

3.1.2 | Case 2

A 62-year-old Caucasian female (body weight 60 kg) presented to the ED and was diagnosed with acute yellow atrophy of the liver. At the moment of ED admission, hepatic parameters reached the following values (Table 1): ALT 1,578 IU/L (range: 0–35 IU/L), AST 2,499 IU/L (range: 0–40 IU/L), TB 25 mg/dL (range: 0.2–1 mg/dL) and direct bilirubin (DB) 15 mg/dL (range: 0–0.25 mg/dL). Clinical examination performed during the hospital stay excluded infections related to HAV, HBV, HCV, CMV and EBV, and results of autoantibodies, as well as Wilson's disease, were negative. Although the patient underwent plasmapheresis, there was no clinical improvement and haematic ammonium reached a value of 115 μmol/L (range: 21–50 μmol/L). Hyperammonaemia was treated with medical enemas and lactulose, and the patient was transferred to the reference transplant centre. This therapy was continued and the patient was monitored in order to decide whether to proceed with the transplant. Finally, the patient's clinical conditions gradually improved (positive dechallenge) and transplant was excluded.

In the ED, the patient reported the consumption of a DS for articular pain, and declared taking 4 tablets/day for the first 5 months, and 3 tablets/day for the subsequent 3 months, for a total of 8 months. As reported on the product label, one tablet of the suspected product contained: *Curcuma longa* L. dry extract (500 mg); *Zingiber officinale* L. dry extract (100 mg); *Piper nigrum* L. dry extract (3 mg); cellulose-derived fibres (300 mg); and stearic-derived fatty acids (62 mg) (brand name CURCUMA COMPLEX®, 120 tablets). The patient was not exposed to any other medical treatment or products, and the exposure to chemical toxic agents, including alcohol, were excluded. The patient was discharged after 18 days of hospitalization with no need for additional therapies.

3.1.3 | Case 3

A 59-year-old Caucasian man (body weight 100 kg) was admitted to intensive care and diagnosed with acute liver disease during concomitant hospital treatment with intravenous amiodarone and azithromycin for heart failure and systemic infection, respectively. During hospitalization, hepatic parameters reached the following values (Table 1): ALT 3,303 IU/L (range: 0–35 IU/L), AST 7,883 IU/L (range: 0–40 IU/L), and gamma glutamyltransferase (GGT) 298 IU/L (range: 5–85 IU/L). The analyses performed were negative for all hepatitis viruses, EBV, and autoantibodies; a reactivation of CMV was observed.

Before being admitted to the hospital, the patient was taking a DS, at a dose of 4 tablets/day for an unspecified period. As reported on the product label, four tablets of the suspected product contained: *Curcuma longa* L. rhizomes powder (70 mg); and *Piper nigrum* L. fruit powder (7 mg) (brand name PIPERINA & CURCUMA PLUS®, 60 tablets, 220 mg each).

At the time of intensive care management, intake of the suspected product was suspended and an improvement in liver function (positive dechallenge) was observed. During hospital stay, the patient was also treated with N-acetylcysteine 600 mg until complete recovery. The hepatic AE resolved completely without the need for any other specific therapy.

3.1.4 | Case 4

A 45-year-old female (body weight 70 kg) visited the ED with symptoms of right hypochondrial pain, gastric pain, jaundice of the sclera and dark urine. Analyses revealed altered liver parameters, in particular (Table 1): ALT 1,846 IU/L (range: 0–35 IU/L), AST 1,277 IU/L (range: 0–40 IU/L), TB 6 mg/dL (range: 0.2–1 mg/dL), GGT 504 IU/L (range: 5–85 IU/L) and alkaline phosphatase (ALP) 274 IU/L (range: 50–136 IU/L). Abdominal ultrasound showed no abnormalities of the liver and gallbladder. HAV, HBV, HCV, CMV and EBV infections were excluded and results of autoantibodies, as well as Wilson's disease, were negative. The patient denied alcohol and paracetamol abuse, and exposure to hepatotoxins (e.g., chemicals, mushrooms, etc.); concomitant medications were excluded.

At the ED, the patient reported that epigastric pain, meteorism and dark urine began 2 months prior in conjunction with consumption of 2-per-day tablets of a DS she had purchased online in order to lose weight. As reported on the product label, the average intake for maximum daily dose of two tablets contained: *Curcuma longa* L. rhizomes dry extract 95% (1,000 mg of which 950 mg of curcuminoids and, in particular, 760 mg of curcumin); *Piper nigrum* L. fruit dry extract 95% (10 mg of which 9.5 mg of piperine); pyridoxine (3.3 mg); riboflavin (2.8 mg); and thiamine (2.7 mg) (brand name CURCUMINA PLUS 95% PIPERINA & VITAMINE B1 B2 B6®, 60 tablets, 800 mg each).

The patient was diagnosed with acute cholestatic hepatitis and treated with N-acetylcysteine 600 mg three times per day. During hospitalization, haematic parameters were strictly monitored and clinicians observed a progressive improvement of liver functions.

3.1.5 | Case 5

A 68-year-old female developed a non-pancreatic cholestatic hepatitis following the use of a product containing Curcuma Phytosome® and

Echinacea angustifolia. The suspected product was prescribed to the patient by a rheumatologist to promote joint function. Two months after starting the suspected product, the patient presented to her general practitioner (GP) due to severe abdominal pain. The GP prescribed blood tests which revealed an increase in transaminases, particularly (Table 1): ALT 257 IU/L (range: 0–35 IU/L), AST 173 IU/L (range: 0–40 IU/L) and GGT 141 IU/L (range: 5–85 IU/L). HAV, HBV, HCV, CMV and EBV infections were excluded. The patient denied alcohol abuse and exposure to hepatotoxic substances. Furthermore, she excluded concomitant treatments.

The patient reported taking a 1-per-day tablet of a DS for a period of 3 months. As reported on the product label, one tablet of the suspected product contained: Curcuma Phytosome® (600 mg of which 200 mg of *Curcuma longa* L. rhizomes dry extract, titrated in curcuminoids, and 400 mg of sunflower phospholipids); and *Echinacea angustifolia* root dry extract (5 mg, titrated in alkylamides) (brand name MOVART®, 30 tablets).

Intake of suspected product was suspended at the time of haematic examinations and the hepatic parameters reverted to normal values over the subsequent 30 days (positive dechallenge). During her stay in the rheumatology unit, an abdominal ultrasound was also performed on the patient which showed gallbladder stones. The AE resolved completely without the need for any specific therapy. It should be noted that the patient reported, during exposure to the suspected product, concomitant exposure to denosumab (60 mg/mL, one injection every 6 months) for postmenopausal osteoporosis.

3.1.6 | Case 6

A 56-year-old Caucasian female (body weight 62 kg) presented to the ED with jaundice and altered liver markers (Table 1): ALT 3,087 IU/L (range: 0–35 IU/L), AST 1,512 IU/L (range: 0–40 IU/L), TB 11.10 mg/dL (range: 0.2–1 mg/dL) and GGT 124 IU/L (range: 5–85 IU/L). The ED diagnosis was acute hepatitis.

In the ED, the patient reported taking 2-per-day tablets of the same DS reported for Case 4 (brand name CURCUMINA PLUS 95% PIPERINA & VITAMINE B1 B2 B6®, 60 tablets, 800 mg each), over a period of 1 month as a food supplement.

The patient's anamnesis did not reveal any history of hepatic disorders or any other relevant concomitant condition, other than pharmacological treatment with oral tablets of bisoprolol 1.25 mg/day. During hospitalization, haematic parameters were strictly controlled and a progressive improvement of the patient's liver functions was observed.

3.1.7 | Case 7

A 61-year-old female (body weight 60 kg) presented to the ED with jaundice and altered liver parameters (Table 1): ALT 2,360 IU/L (range: 0–35 IU/L), AST 1,336 IU/L (range: 0–40 IU/L) and DB 3.9 mg/dL (range: 0–0.25 mg/dL). Clinical examination performed during hospital stay excluded infections related to HAV, HBV, HCV, CMV and EBV, and results of autoantibodies, as well as Wilson's disease, were negative. An abdominal ultrasound performed during hospitalization did not highlight any abnormality of the liver or gallbladder. The patient was diagnosed with acute cholestatic hepatitis.

At the ED, the patient reported she had been consuming 1-per-day tablet of a DS for a period of 2 weeks as an antioxidant. As reported on the product label, two capsules of the suspected product contained: *Curcuma longa* L. rhizomes dry extract 95% (500 mg of which 475 mg of curcumin); and *Boswellia serrata* Roxb. gum-resin dry extract 65% (200 mg of which 130 of boswellic acids); *Lithothamnion calcareum* seaweed thallus (20 mg) (brand name W-CURCUMA+®, 60 capsules). Intake of the suspected product was suspended and hepatic parameters reverted to normal values (positive dechallenge).

3.2 | Systematic review

We included 13 studies for a total of 23 cases (Figure 1). Once the articles were selected, the following significant data were extracted: article, country, number of patients, gender, age (years), adverse events, diagnosis, symptoms, clinical outcome, clinical history, concomitant drugs, and exposure to CL before onset of symptoms. Characteristics of the analysed studies are reported in Table 2.

All articles, except one,[36] reported the presence of one or more concomitant medications and/or products. Elevation of liver enzymes was reported as a preferred term in all patients, and in three of these cases the elevation of transaminases was described as asymptomatic. Length of exposure to CL varied among patients; their symptoms developed between 2 weeks and 10 months of exposure. Out of 23 patients, 17 improved after CL was withdrawn (positive dechallenge), confirming a possible causal relationship between CL exposure and liver injury. Two patients died, one patient was hospitalized and information on clinical outcome was not available for three patients.[42] Moreover, information on gender was not available for nine patients. Liver serum values of cases retrieved by the systematic review are listed in Supporting Information Table S2.

RUCAM[28,29] was used in the majority of the included papers to estimate causality between the observed AEs and CL assumption. Seven cases[23,33,37,41,43,44] 38 were judged as highly probably/probably and one case[22] was judged as possibly related to CL. Only Lukefahr and colleagues[23] used another algorithm to evaluate their case—simplified criteria for the diagnosis of autoimmune hepatitis[45]—with a result of a "probable" causal relationship between the event of autoimmune hepatitis and CL. Overall, the studies included in the systematic review showed a moderate to high quality (Supporting Information Table S3).

4 | DISCUSSION

In Italy, from the end of 2018 to mid-2019, a cluster of acute non-infectious hepatitis, including severe cases,[24] was observed and these events were related to the consumption of CL-containing DS manufactured by various producers. As far as we know, this is the first

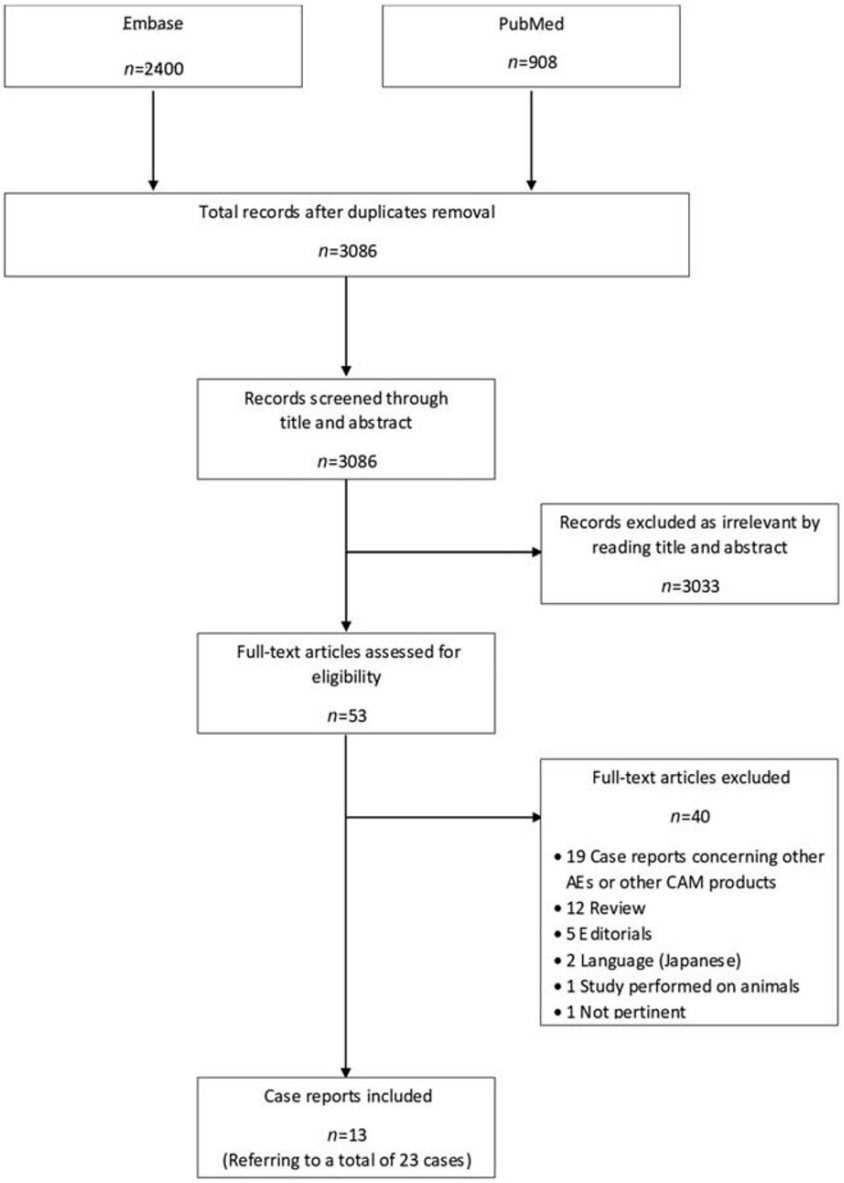

FIGURE 1 Systematic review flowchart

study to attempt to analyse and describe the events that occurred in Italy, with attention to those collected in Tuscany. Moreover, this is the first study presenting evidence on CL-related hepatotoxicity through a systematic review of case reports and case series. Certainly, a full description of all cases recorded in Italy would be of great value for the scientific community worldwide.

The awareness of potential hepatotoxicity associated with DS is increasing. The last decades have shown that herbal medicines may cause a large spectrum of liver injury, affecting all cells present in the liver and biliary tree, and ranging from mild asymptomatic liver enzyme elevation to acute hepatitis. In general, physicians may consider herbal and DS as potential causative agents associated with liver injury.[46]

Curcumin, a polyphenolic yellow substance, is the major constituent of CL. It comes from the rhizome of the plant and, since ancient times, has been frequently used for different alimentary and therapeutic purposes.[1] The presumed activities of curcumin, based on in vitro and in vivo studies[47] are antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral, hypoglycaemic and wound healing. However, the clinical trials published so far have not yet produced sound proof of efficacy; thus, curcumin has not yet been approved as a therapeutic agent, probably because of its low bioavailability, instability at physiological pH, insolubility in water, slow uptake by cells and rapid metabolism inside cells. In terms of pharmacodynamic effects, curcumin is a highly pleiotropic molecule able to interact with several molecular targets such as proteins, enzymes, DNA, RNA and carriers.[47] On the LiverTox database, a free online source for information on herb/drug-induced liver injury,[48] turmeric is considered a possible cause of clinically apparent liver injury (likelihood score: D).

Many studies have investigated the safety of CL and curcumin.[1] These studies have been conducted on cell culture, animals and, some of them, on healthy people and patients. According to these studies,

TABLE 2 Systematic review: Characteristics of the studies included in the systematic review

Article	Country	No. of patients	Age/gender	Adverse event and diagnosis	Symptoms
Abdallah, 2019[33]	USA	1	51 years/F	Drug-induced liver injury with turmeric being the culprit	Right upper quadrant pain, fatigue, dark urine, elevated liver enzymes, scleral jaundice and mild epigastric tenderness
Costa, 2018[34]	Portugal	1	67 years/M	Acute toxic hepatitis due to pharmacokinetic interaction between turmeric and paclitaxel and a contaminated *Chlorella* dietary supplement	Pruritus and erythematous lesions, initially treated with anti-histamine therapy, asthenia, anorexia, jaundice and choluria, elevated liver enzymes
Fernández-Aceñero, 2019[35]	Spain	1	78 years/F	Acute liver injury with features suggestive of cirrhosis and portal hypertension at abdominal ultrasonography. Possible interaction between etoricoxib and CL	Asthenia, epigastric pain, mild conjunctival icterus
Gasbarrini, 2019[36]	Italy	4	25–45 years/3F and 1 M	Anorexia, dyspepsia, hyposthenia, belching, meteorism and epigastric pain. Hepatitis; hepatocytonecrosis and cholestasis	Hypertransaminasemia up to 3–6 times with respect to normal value, and increasing of GGT up to 4–8 times the norm
Imam, 2019[37]	USA	1	78 years/F	Curcumin-induced hepatocellular liver injury	Jaundice and acholic stools
Lee, 2020[38]	USA	1	55 years/F	Curcumin-induced hepatocellular liver injury	Nausea, vomiting, dark urine, jaundice
Lim, 2017[39]	USA	1	45 years/F	Drug-induced granulomatous hepatitis	Incidental liver masses noted during a non-contrast computed tomography
Luber, 2019[22]	Australia	2	52 years/F	Severe liver injury	Nausea, pruritus, painless jaundice, pale stools, and dark urine
			55 years/M	Severe liver injury	Asymptomatic transaminitis; diffuse steatosis at abdominal ultrasonography
Lukefahr, 2018[40]; Funk, 2017[41]	USA	1	71 years/F	Autoimmune hepatitis	Asymptomatic transaminitis; curcuminoids accumulation on liver biopsy, elevated IgG levels, positive antibody titres for atypical pANCA and smooth muscle actin
Nergård, 2009[42]	Norway	9	NR	1 patient diagnosed with hepatitis; 4 cases reported liver toxicity; 4 cases reported hepatic adverse events	Altered liver enzymes (4 cases)
Suhail, 2019[43,44]	USA	1	61 years/F	Drug-induced liver injury (panlobular hepatitis with early parenchymal collapse at liver biopsy)	Fatigue, dark urine, polyarthralgias, right upper quadrant abdominal tenderness, transaminitis

GGT, gamma glutamyltransferase; NR, not reported; pANCA, peri-nuclear anti-neutrophil cytoplasmic antibody.

TABLE 2 (Continued)

Article	Clinical outcome	Clinical history	Concomitant drugs	Exposure to CL before onset of symptoms
Abdallah, 2019[33]	Improvement after CL withdrawn	Polyalergy and allergic rhinitis, anxiety	Sertraline 25 mg/day for 2 years; multivitamins, primrose oil and omega 3 dietary supplements (occasionally); cetirizine and methylprednisolone 2 weeks before patient's evaluation due to an allergic reaction	2 months 1 cps/day, 500 mg (composition: 400 mg turmeric powder, 50 mg turmeric extract, 50 mg organic ginger powder each capsule)
Costa, 2018[34]	Improvement after CL and *Chlorella* withdrawn	Lung cancer, pulmonary emphysema, type 2 diabetes, dyslipidaemia, and benign prostatic hyperplasia	Paclitaxel 165 mg/m^2 + carboplatin 275 mg/m^2 bi-monthly; *Chlorella* (520 mg/day); metformin/sitagliptin association; alfuzosin; atorvastatin; budesonide; formoterol; tiotropium bromide; *Silybum marianum* (total of 13.5 mg silymarin/day); zinc sulphate (5.5 mg); selenium (50 μg); colostrum (650 mg/day)	Around 38 days 15 g/day
Fernández-Aceñero, 2019[35]	Improvement after CL withdrawn and treatment with prednisone	Osteoarthritis	Etoricoxib 60 mg/day 1 month before symptoms onset	NR, the patient reported long term use
Gasbarrini, 2019[36]	Improvement after CL withdrawal	NR	Patients reported not to be exposed to other medications or dietary supplements	1 month for all patients
Imam, 2019[37]	Improvement after CL withdrawal	Type 2 diabetes mellitus, essential hypertension	Aspirin (81 mg), citalopram, losartan, metformin, oxybutynin, simvastatin (used for 2 years then stopped and replaced with curcumin)	1 month
Lee, 2020[38]	Improvement after CL withdrawal	Hashimoto's thyroiditis	Famotidine, aluminium hydroxide-magnesium hydroxide, simethicone, levothyroxine	3 months
Lim, 2017[39]	Improvement after CL, multivitamin and dehydroepiandrosterone withdrawn	Essential hypertension, Hashimoto's thyroiditis, and depression	Lisinopril; levothyroxine; atorvastatin; duloxetine; dehydroepiandrosterone; not specified multivitamin	NR
Luber, 2019[22]	Improvement after CL withdrawn; positive rechallenge after a new CL assumption and consequent improvement after a final cessation	Oligoarticular osteoarthritis	Flaxseed oil; diclofenac (occasionally); cholecalciferol 50 mcg/day; ascorbic acid 500 mg/day; levonorgestrel 52 mg intrauterine device	1 month 1 tablet/day (composition: 375 mg curcuminoids; 4 mg black pepper each tablet)
	Improvement after CL withdrawn.	Idiopathic thrombocytopenic purpura, hypertension, gout, and osteoarthritis	Telmisartan; atenolol; lercanidipine.	5 months
Lukefahr, 2018[40]; Funk, 2017[41]	Improvement after CL withdrawn	Hypothyroidism, Raynaud's syndrome, osteoarthritis, hypertension, dyslipidaemia, irritable bowel syndrome, and diverticulosis	Amplodipine; metoprolol; atenolol; benazepril; levothyroxine; meloxicam; estradiol, loratadine; diphenhydramine; aspirin; calcium; vitamin D; multivitamin	52 weeks

TABLE 2 (Continued)

Article	Clinical outcome	Clinical history	Concomitant drugs	Exposure to CL before onset of symptoms
			dietary supplement; fish oil; alpha-galactosidase, invertase, lysine, alfalfa powder, glucosamine, and chondroitin dietary supplement; high fibre dietary supplement with vitamins, minerals and grape seed exctract	
Nergård, 2009[42]	Death (2 cases); improvement after CL withdrawn (3 cases); hospitalization (1 case); no information reported (3 cases). Adulterated product with nimesulide	NR	Other drugs associated with increase in liver enzymes (3 cases)	2 weeks to 6 months
Suhail, 2019[43,44]	Improvement after CL withdrawn	Benign polycystic liver disease	Naproxen and ergocholecalciferol (4 years of use)	6 months

GGT, gamma glutamyltransferase; NR, not reported; pANCA, peri-nuclear anti-neutrophil cytoplasmic antibody.

standardized powder and extract of CL are generally safe for human use even at high doses (e.g. oral administration of curcumin at the dose of 6 g/day for 4–7 weeks). Curcumin was also found to be safe at certain doses in intravenous administration in humans. In addition, curcumin is a non-mutagenic and non-genotoxic agent.[49,50] In pregnancy, curcumin was found to be safe in animals but more studies are needed to confirm its safety in pregnant women.[51]

The mechanism of toxicity of curcumin on the liver is not clearly defined. Acute and subchronic toxicity of CL in animals were reported by Deshpande et al.[52] In their investigation, oral toxicity of CL and ethanolic CL extract was studied in female Swiss mice and Wistar rats fed with CL (0, 1 and 5%) and ethanolic CL extract (0, 0.05 and 0.25%) through diet for 14 and/or 90 days. The administration of a high dose of CL (5%) for a longer duration (90 days) showed alterations in absolute and/or relative liver weight and hepatotoxicity. In mice, lower doses of CL (0.2 or 1%) for 14 days also showed hepatotoxicity. Funk and colleagues,[53] through their experiments, reported elevations in serum ALT in female rats with streptococcal cell wall-induced arthritis, consistent with hepatocellular damage.

Safety and toxicity of CL/curcumin in humans have also been evaluated. In the study by Na and colleagues[54] no serious adverse events were reported in 100 diabetic and obese patients who received 300 mg/day of curcuminoids (36.06% curcumin, 18.85% demethoxycurcumin and 42.58% bisdemethoxycurcumin) over a 3-month period, but changes in liver enzymes and biochemical parameters of blood were observed.

Although curcumin has been studied for its benefits in a number of hepatic pathologies,[55] the exact mechanism by which curcumin could induce liver damage is still not completely understood. Liver function test derangement has been reported in approximately 5% of cases in randomized controlled trials,[23] particularly when treatment duration was less than 1 month. This incidence, however, is consistent with the notion that CL-induced liver injury may be idiosyncratic, thus without a clear relationship between degree of liver injury and dosage. Considering curcumin metabolism, which comprehends different biotransformations and takes place in the cytosol of bowel and hepatic cells,[56] how it could affect mitochondrial dysfunction, oxidative stress, hepatic transporters modulation, and reactive metabolites production, has yet to be addressed.

The clinical manifestations observed in our patients, particularly the absence of specific signs and symptoms such as rash, fever, lymphadenopathy, angioedema, arthralgia, eosinophilia and/or a typical lymphocytosis, rules out the possibility of an herb-induced immunological reaction.[48] The cases we have described were associated with CL formulations with high bioavailability, such as those in which CL was associated with piperine.[1] This is an important detail since the events that occurred in Tuscany seem to be characterized by the use of CL formulations with high bioavailability, often in association with piperine, and it is possible that safety profiles of these associations are still not well known. In fact, piperine enhances curcumin absorption and it might determine a mechanism of direct toxicity, perhaps favoured by a higher genetic individual susceptibility.[24]

Another hypothesis of CL-containing DS toxicity takes into account the presence of synthetic curcumin. In fact, the impact of substituting (synthetic) curcumin for naturally occurring curcuminoids is not known, both in term of efficacy and safety. Since natural curcumin has a low stability in biological fluids, the presence of synthetic curcumin could raise the possibility that purified curcumin *vs* turmeric-derived curcuminoid mixtures may not be bioequivalent.[57] Moreover, the negative association of turmeric DS cost with a high percentage of curcumin suggests that the likelihood of purchasing a product that may contain synthetic rather than turmeric-derived curcuminoids may be higher with less expensive products. Finally, the production of synthetic curcumin may lead to the presence of degradation compounds (i.e., ferulic acid, acetone and vanillin) and solvent residuals (i.e., isopropanol, ethyl acetate, acetone, methanol, ethanol and hexane) in the CL-containing DS available on the market, which may contribute to their final risk profile in humans.[58]

Another consideration takes into account CL dosages in food supplements reported in our case series. In fact, CL dose varied among the different DS, but it was always higher than the total amount of turmeric that subjects usually consume through common culinary use. Even CL itself contains more than 200 active compounds, 64 of which have been associated with hepatotoxicity.[59] In this context, and considering that available DS usually contain several ingredients, the active substance specifically responsible for liver damage could be difficult to identify.[25] Furthermore, while clinical studies may assess pure curcumin compounds, the products available to patients in community pharmacies, nutritional food stores and online shops contain varying concentrations of curcumin plus numerous additives, potentially accounting for differing real-life risk profiles.[22] Thus, it would be important to know where certain products were purchased. Unfortunately, for only two of the Tuscan patients did we have information about the purchase of suspected product. One patient bought the DS online, and the other one received a prescription from his rheumatologist. In fact, it is not always easy to find this information due to the lack of a specific field in the AE report form.

The case series described in the present article suggests a potential causal association between consumption of CL-containing DS and development of acute liver injury, in particular non-infectious hepatitis. Although in some cases liver damage progressed more slowly, this association was supported by the positive dechallenge observed in most cases, particularly in terms of transaminase normalization from cessation of the suspected product. The duration of treatment was different among cases, ranging from 2 weeks to 8 months. For one patient only, information on the duration of exposure to CL was not available. Taking into account the time to onset proposed by EASL Clinical Practice Guidelines for drug-induced liver injury,[46] HILI ranges in presentation with latency of 6–14 weeks after treatment initiation, but may also occur after longer periods of treatment and occasionally after discontinuation of the suspected DS. Physicians should always consider the time to onset also for CL-containing DS, particularly for the definition of delayed events.

Several liver diseases (e.g. hepatitis, cirrhosis, etc.), which are possible alternative causes of liver damage, have been excluded both for the patients in Tuscany (except one) and for all the cases reported in the literature. Unfortunately, among Tuscan patients, the presence of hepatitis E virus has never been evaluated. This can be considered as another limitation. It is worth noting that we cannot completely exclude the presence of patients' genetic predisposition leading to hepatic toxicity,[25] such as metabolic enzyme polymorphisms promoting toxic accumulation of CL and/or piperine metabolites.

The risk of herb–drug interaction leading to hepatotoxicity[25] cannot be completely excluded in the cases described here. Curcumin demonstrated an inhibitory effect on a number of cytochrome P450 subtypes,[60,61] thus CL can potentially interact with some conventional drugs such as anticoagulants, antibiotics, cardiovascular drugs, anticancer drugs and antidepressants.[62,63] Among the cases collected in Tuscany, three subjects reported being exposed to one or more concomitant medications at the time of hepatic AE onset. With regard to cases identified through the systematic review, the majority of patients were concomitantly exposed to at least one of the medicines listed above. Therefore, clinical attention to interactions is important when prescribing CL simultaneously with conventional drugs, especially in patients suffering from chronic diseases who are generally exposed to several medications.[64]

As described by Nergård et al.[42] and Navarro et al.,[65] hepatotoxicity may also be caused by an accidental or deliberate adulteration or mislabelling of herbal or drug supplements. Nevertheless, the analyses required by the Italian Ministry of Health on samples of each product reported in our case series did not indicate any presence of contaminants or adulterants.

Of note, since this study is based on AE reports, it presents another limitation that includes inaccurate and incomplete information, mainly related to lack of clinical data. Given that, the absence of information that was not listed in AE reports and that might have influenced the clinical evaluation of each report (i.e., the lack of information on previous and/or current patient medical conditions which could affect the clinical evaluation of each case) could not always be excluded. For example, the lack of blood parameters for some patients may have affected the application of the RUCAM score.

In response to the hepatitis outbreak linked to CL-based preparations, the Italian Ministry of Health, in the Decree published on July 26, 2019, made it mandatory to insert the following warnings on the labelling of all food supplements containing preparations and extract of one of the Curcuma species: "*In the event of alterations in liver function, biliary or calculosis of the biliary tract, the use of this product is not recommended*", and "*If you are taking other pharmaceutical treatments, it is appropriate to seek the advice of a physician*". Moreover, the Ministry has also forbidden the possibility of reporting on the label any indications about physiological effects regarding the "hepatic function", "digestive function" and "digestive system". All stakeholders are therefore invited to update the labelling of their food supplements so that their products comply with the new Italian requirements.

5 | CONCLUSIONS

Based on our results, liver injury associated with CL intake is a concrete risk, needing further attention by clinicians. The scientific community, as well as health authorities across countries, should promote premarket quality and safety approval checks and post-marketing surveillance of such products, particularly those containing CL, as well as spontaneous reporting of suspected adverse reactions. Patients should always tell their healthcare providers, including their doctors, pharmacists and dieticians, about which DS they are taking so that they can discuss what is best for their overall health.

ACKNOWLEDGEMENTS

We would like to express our special thanks to Dr David Coletta, Dr Anna Ciaramelli, Dr Maria Luisa Migliaccio, Dr Susanna Camilletti and Dr Lucia Parisi for their contributions to the present manuscript, and Dr Antonella Vincenti for providing additional clinical information on cases reported in Tuscany. Moreover, we would like to thank Dr Carolina Mosoni, Dr Fiorenza Bonvicini, Prof. Giovanni Gasbarrini, Dr Cecilie Sogn Nergård and Prof. Janet Funk for their kind response to our requests.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CONTRIBUTORS

The study design was contributed by N.L. and G.C., with assistance from the rest of the authors. Data acquisition was performed by N.L., G.C., F.M.I., I.I., V.B., C.L. and G.M. Data interpretation was performed by N.L., G.C., V.M., E.G., F.F. and A.V., with assistance from the other authors. The manuscript was written primarily by N.L. and G.C., with assistance from the other authors, and revised by F.M.I., G.M., F.F. and A.V. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Italian National Institute of Health (Istituto Superiore di Sanità, ISS). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the Italian National Institute of Health (ISS).

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SUPPORTING INFORMATION

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

How to cite this article: Lombardi N, Crescioli G, Maggini V, et al. Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports. *Br J Clin Pharmacol*. 2020;1–13. https://doi.org/10.1111/bcp.14460