

Supplementary Materials for

Turmeric (*Curcuma longa* L.) food supplements and hepatotoxicity: an integrated evaluation approach

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Supplementary Table 1S

Summary information of the reports

Table 15
Summary information of the reports

Patient ID	Date onset reaction	Date report	Reaction	Sex Age	Reason	Concomitant drugs/ concomitant conditions	Ingredients	Composition/ dose	Recommended dose	Taken dose/ length	Outcome	Dechallenge/ rechallenge	WHO-Causality Assessment
1	10/11/18 Toscana	4/12/18 NIH	Hepatitis	W 55 Years	Detoxification	NO	Curcuma longa dry extract 1:4 and Turmeric rhizome powder	For 6 capsules (3 g): Curcuma longa dry extract 2400 mg; turmeric powder 540 mg	3-6 capsules/day	3 capsules/day for 2 months	Complete resolution	Positive / not reported	Probable
2	26/11/18 Toscana	07/12/18 NIH	Acute yellow liver atrophy	W 62 Years	Arthritis	NR	Curcuma longa dry extract 95% in curcumin; Zingiber officinalis (ginger) dry extract 5% in gingerols; Piper nigrum dry extract 95% in piperine	For 3 capsules (4 g): Curcuma longa dry extract 1500 mg; ginger dry extract 300 mg; Piper nigrum dry extract 9 mg	3 capsules/day	3-4 capsules/day for 7 months from April 2018 to November 2018	Not reported	Positive / not reported	Probable
3	01/12/18 Toscana	15/05/19 VigiErbe	Cholestatic hepatitis	W 68 Years	Senile osteoporosis	Denosumab (Prolia)	Turmeric phytosome (titrated in curcuminoids) Echinacea angustifolia (titrated in alkylamides)	-	1-2 capsules/day	1 capsule/day for 1 month from 1 November 2018 to 1 December 2018	Complete resolution	Positive / not reported	Probable
4	12/18 Lombardia	22/05/19 NIH	Cholestatic hepatitis	W 50 Years	Self-prescription	NO	Curcuma longa dry extract 95% in curcuminoids; Piper nigrum dry extract 95% in piperine	For 1 capsule: turmeric 400 mg of which 380 curcuminoids; 30 mg black pepper of which 28,5 mg piperine	3 capsules/day	unknown dose, for 2 months from 18 October 2018 to 18 December 2018	Complete resolution	Positive / not reported	Probable
5	05/01/19 Lazio	02/03/19 VigiErbe	Acute hepatitis	W 70 Years	hypercholesterolemia	NR	Red rice, berberine, melograno, turmeric	Red rice fermented with Monascus purpureus, berberis dry extract titrated 87,3% in berberine hydrochloride, turmeric dry extract 95% in total curcuminoids, melograno dry extract titrated 40% in punicoside, coenzyme Q10/ 1 capsule: red rice fermented with Monascus purpureus titrated 3% in monacolin K (total 333 mg equal to Monacolin K 10 mg), berberis dry extract titrated 87,3% in berberine hydrochloride (170 mg equal to 148 mg berberine hydrochloride), turmeric dry extract titrated 95% in total curcuminoids (turmeric 50 mg equal to curcumin 47,5 mg), pomegranate dry extract titrated 40% in punicosides (50 mg equal to punicoside 20 mg), coenzyme Q10 2 mg	1 capsule at night during/after meal for at least 60 days	2 Years from 01/01/17 to 05/01/19	Complete resolution	Positive / not reported	Possible
6	09/01/19 Friuli-Venezia-Giulia	16/01/19 NIH	Elevated serum liver transaminases, epigastric pain	W 63 Years	Food supplement	Ramipril and Maalox (magnesium hydroxide and aluminium oxide hydrated/ arterial hypertension)	-	-	-	8 days from 01/01/19 to 09/01/19	Complete resolution	Positive / not reported	Possible
7	12/01/19 Lombardia	22/05/19 VigiErbe	Acute hepatitis	W 49 Years	Weight loss	NO	Turmeric dry extract titrated 95% in curcumin; Pepe nero dry extract titrated 95% in piperine	For 1 capsule (?): turmeric dry extract 350 mg; black pepper dry extract 7 mg	1 capsule/day	1 capsule/day for 6 months from 01/08/18 to 21/01/19	Not reported	Not reported / not reported	Probable
8	10/01/19 Lombardia	15/05/19 poison control center	Acute cholestatic hepatitis, icterus	W 46 Years	Healthy product	Ketoprofen (OKI)	turmeric, ginger	turmeric 80 g, ginger 80 g	1/2 teaspoon of turmeric + 1/2 teaspoon of ginger in 1 glass of warm water, consumed a package of 80g	2 months and 20 days from 20/10/18 to 10/01/19	Complete resolution	Positive / not reported	Possible
9	17/01/19 Lombardia	29/03/19 poison control centre	Acute cholestatic hepatitis	W 37 years	Weight loss	Paracetamol (Tachipirina) Neurapass forte (hypericum, passionflower, valerian) Reduflux (brown seaweed), Griffonia plus (20% 5-HTP)	Curcuma longa dry extract 95% in curcumin; Piper nigrum dry extract 95% in piperine Vitamins B6, B2 and B1	2 capsules (2 g): turmeric rhizome dry extract 1000 mg bringing in curcuminoids 950 mg, bringing in curcumin 760 mg, black pepper fruits dry extract 10 mg bringing in piperine 9,5 mg	max 4 capsules/day	4 capsules/day for 1 month from 15/12/18 to 17/01/19	Complete resolution	Positive / not reported	Possible

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Patient ID	Date onset reaction	Date report	Reaction	Sex Age	Reason	Concomitant drugs/ concomitant conditions	Ingredients	Composition/ dose	Recommended dose	Taken dose/ length	Outcome	Dechallenge/ rechallenge	WHO-Causality Assessment
10	10/03/19 Lombardia	29/03/19 poison control centre	Cholestatic hepatitis	W 29 years	Weight loss	Ibuprofen (Brufen), thio-colchicoside (Muscoril)	Curcuma longa dry extract 95% in curcuminoids and 76% in curcumin; Piper nigrum dry extract 95% in piperine, Vitamins B6, B2 and B1	For 2 capsules (1,6 g): turmeric dry extract 1000 mg bringing in curcuminoids 950 mg and curcumin 760 mg; Piper nigrum dry extract 10mg bringing Piperine 9,5mg	max 2 capsules/day	1 capsule/day occasional intake (60 capsules in 3 months) from 15/12/19 to March 2019	Not reported	Positive / not reported	Possible
11	23/03/19 Veneto	29/03/19 poison control centre	Cholestatic hepatitis	W 58 Years	NR	Simvastatin, olmesartanmedoxomil (Plaunac) Phytodrena (green tea leaves dry extract, caffeine, asparagus root dry extract, weat grass rhizome, burdock root dry extract, dandelion root dry extract; Frama)	Curcuma Meriva®; curcumin 95%; Piperine 95%	For 1 capsule: Curcuma Meriva 260 mg (Curcuma longa dry extract (95 % in curcuminoids); Piper nigrum dry extract 5mg (95% in piperine)	-	2-3 capsules/day for two-and-a-half months	Not reported	Not reported/ not reported	Possible
12	02/04/19 Emilia-Romagna	03/06/19 ViggiErbe	Elevated serum liver transaminases	W 69 Years	Osteoarthritis	NO	Turmeric, phytosome (titrated in curcuminoids) Echinacea angustifolia (titrated in alkylamides)	-	1-2 cps/day	1 capsule/day for 1 month from 06/03/19 to 02/04/19	Complete resolution	Positive / not reported	Probable
13	03/04/19 Lombardia	21/05/19 ViggiErbe	Acute cholestatic hepatitis	W 53 Years	NR	NR	Curcumin 95%; Piperine 95%	For 1 capsule: turmeric dry extract 400 mg bringing in curcumin 380 mg; Piper nigrum dry extract 2,5 mg (piperine 2,375 mg)	1-2 capsules/day	3 months from February 2019 to April 2019	Not reported	Not reported/ not reported	Probable
14	18/04/19 Umbria	22/05/19 NIH	Acute cholestatic hepatitis	W 71 Years	Joint pain	Amoxicillin + clavulanic acid, Vertiser (betahistinebichloride), telmisartan	Curcuma longa L., rhizome dry extract titrated 95% in total curcuminoids, Boswellia serrata Roxb., dry extract titrated 75% in boswellic acids	For 1 sachet: turmeric 210 mg of which 200 mg curcuminoids; Boswellia 200 mg of which 150 mg boswellic acids	1 sachet/day	1 sachet/day for 15 days from 09/04/19 to 24/04/19	Resolution with sequelae	Positive / not reported	Possible
15	01/05/19 Campania	24/05/19 NIH	Cholestatic hepatitis, icterus	W 46 Years	Weight loss	NO	Turmeric dry extract and piperine	-	4 capsules /day	4 capsules/day for 5 weeks from 10/03/19 to 01/05/19	Persistent reaction	Positive/ not reported	Probable
16	03/05/19 Toscana	15/05/19 NIH	Acute hepatitis	W 56 Years	Food supplement	Bisoprolol	Curcuma longa dry extract 95% in curcuminoids and 76% in curcumin; Piper nigrum dry extract 95% in piperine, Vitamins B6, B2 and B1	For 2 capsules (1,6 g): turmeric dry extract 1000 mg bringing in curcuminoids 950 mg and curcumin 760 mg; Piper nigrum dry extract 10 mg bringing Piperine 9,5 mg	max 2 capsules /day	2 capsules/day for 1 month from 24/03/19 to 24/04/19	Persistent reaction	Negative/ not reported	Possible
17	06/05/19 Toscana	15/05/19 ViggiErbe	Acute hepatitis	W 45 Years	Weight loss	NR	Curcuma longa dry extract 95% in curcuminoids and 76% in curcumin; Piper nigrum dry extract 95% in piperine, Vitamins B6, B2 and B1	For 2 capsules (1,6 g): turmeric dry extract 1000 mg bringing in curcuminoids 950 mg and curcumin 760 mg; Piper nigrum dry extract 10 mg bringing Piperine 9,5 mg	max 2 capsules/day	1 capsule/day for 2 months from 05/03/2019 to 05/05/2019	Not reported	Not reported/ not reported	Probable
18	15/05/19 Lombardia	24/05/19 ViggiErbe	Acute hepatitis	M 48 Years	NR	NO	a. methylsulfonylmethane, hydrolysed collagen turmeric dry extract, Boswellia dry extract, myrrh dry extract, glucosamine, chondroitin sulphate arginine; lysine, vitamin C b. Glucosaminehydrochloride, chondroitin sulphate; Bio-curcumin BCM-95 Curcuma longa titrated 95% in curcuminoids	a. in 2 sachet: turmeric dry extract 200 mg; Boswellia dry extract 200 mg; myrrh 100 mg - b. bio-curcumin 50 mg	a: 1-2 sachet/day b: 1 capsule/day	a. 1-2 sachets for 2 months, b. for 3 days	Not reported	Not reported/ not reported	a. Probable b. Possible
19	15/05/19 Lazio	09/06/19 ViggiErbe	Acute hepatitis	W 55 years	Weight loss	Garcinia 1000, Eliquis (apixaban), Almarytm (flecainide), Eutirox (levothyroxine/ Hypothyroidism (secondary to hashimoto's thyroiditis), atrial fibrillation since 2016, atrial ablation	Curcuma longa dry extract 95% curcuminoids, black pepper 95% piperine	1. unknow 2. Curcuma Curcuma longa rhizome) 360mg dry extract titrated 95% curcuminoids; Black pepper (Piper nigrum L.) fruit dry extract 80 mg titrated. 95% piperine;	2. 1 capsule before lunch and 1 capsule before dinner	1. from 15/04/19 2. From the beginning of May	Complete resolution	Positive / not reported	2. Possible
20	19/05/19 Piemonte	29/05/19 ViggiErbe	hyperbilirubinemia, icterus	W 50 Years	Weight loss	NR	Turmeric dry extract and piperine	-	4 capsules/day	2 capsules/day for 1 month from April 2019 to 19/05/2019	Complete resolution	Not reported / not reported	Probable

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21	23/05/19 Calabria	31/05/19 NIH	Acute cholestatic hepatitis	W 50 Years	Weight loss	NO	Turmeric rhizome dry extract, 95% curcuminoids black pepper fruits dry extract, 95% piperine	Turmeric rhizome dry extract 900 mg, of which curcuminoids 855 mg, black pepper fruits dry extract 10 mg, of which piperine 9,5 mg	2 capsules/day	90 capsules for a month and a half from April 2019 to May 2019	Complete resolution	Positive / not reported	Probable
22	28/05/19 Toscana	01/06/19 NIH	Acute hepatitis	M 59 Years	NR	Amiodarone, azithromycin	Piperine and turmeric	?	?	4 capsules/day ?	Not reported	Positive / not reported	Not classifiable/ Await further data
23	07/02/2019 Lombardia	17/06/2019 VigiErbe	Elevated serum liver transaminases	W 30 Years	NR	Tisane: hydroalcoholic extract of: fennel fruits, coriander fruits, cumin fruits; ginger rhizome (freeze-dried extract), fennel essential oil	1. ginger and turmeric 2. dandelion and turmeric	1. ginger 50%, turmeric 36% 2. aromatic herbs 46% (chamomile flowers and fennel flowers), dandelion 31,6%, turmeric 22,4%	1. NR 2. 2-3 cups/day (1 sachet in 200 ml)	1. 6 months from 01/10/2018 to 22/03/2019 2. from 2018 to March 2019	Complete resolution	Positive / positive	1.Probable 2. Probable
24	05/2019 Lombardia	18/06/2019 VigiErbe	Elevated serum liver transaminases	M 57 Years	NR	Cholecystectomy due to acute cholecystitis in 2017	Curcumin and piperine	Turmeric rhizome (Curcuma longa) 40 mg titrated 95% curcuminoids, black pepper fruits (Piper nigrum L.) powder 20 mg	2 capsules at lunch and 2 at dinner	4 capsules/day for 3 months from 15/04/2019 to June 2019	Not reported	Positive/ not reported	Probable
25	23/05/2019 Lombardia	18/06/2019 VigiErbe	Liver failure	W 63 Years	NR	NR	Curcuma longa dry extract 95% in curcuminoids and 76% in curcumin; Piper nigrum dry extract 95% in piperine, Vitamins B6, B2 and B1	For 2 capsules (1,6 g): turmeric dry extract 1000 mg bringing in curcuminoids 950 mg and curcumin 760 mg; Piper nigrum dry extract 10 mg bringing Piperine 9,5 mg	max 2 capsules/day	From April 2019 to 23/05/2019	Complete resolution	Not reported/ not reported	Probable
26	29/05/2019 Campania	10/07/2019 NIH	Elevated serum liver transaminases	M 56 Years	NR	Non alcoholic hepaticsteatosis	Milk Thistle, Curcuma Meriva® phytosome	Milk Thistle 800 mg titrated 80% in silymarin 640 mg, Turmeric phytosome (Meriva®) rhizome dry extract (Curcuma longa and soy lecithin titrated 18% in curcuminoids (36 mg)	1 capsule/day	1 capsule/day from 01/04/2019 to 29/05/2019	Not reported	Not reported/ not reported	Probable
27	12/06/2019 Toscana	06/07/2019 VigiErbe	Acute cholestatichepatitis	W 61 Years	Antioxidant	Renaltubularnecrosis	Curcuma longa L. rhizome dry extract 95% in curcumin	Boswellia serrata Roxb dry extract 65% in boswellic acids, lithotamnion calcareum (thallus) Curcuma longa L. rhizome dry extract 95% in curcumin	1 capsule twice a day away from meals	1 capsule/day from 02/05/2019 to 20/05/2019	Complete resolution	Not reported/ not reported	Probable
28	17/06/2019 Lombardia	26/06/2019 VigiErbe	Elevated serum liver transaminases, hyperbilirubinemia	W 44 Years	Vitamin supplement, digestion	NR	Curcuma longa dry extract 95% in curcuminoids and 76% in curcumin; Piper nigrum dry extract 95% in piperine, Vitamins B6, B2 and B1	For 2 capsules (1,6 g): turmeric dry extract 1000 mg bringing in curcuminoids 950 mg and curcumin 760 mg; Piper nigrum dry extract 10 mg bringing Piperine 9,5 mg	max 2 capsules/day	1 capsule after meals from 20/05/2019 to 24/05/2019	Complete resolution	Not reported/ not reported	Probable