

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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| 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 Vigierbe | 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 Vigierbe | 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 Vigierbe | 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 Vigierbe | 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 Vigierbe | 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. unknown 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 Vigierbe | 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 cholestatic hepatitis | 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 |