European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON *CURCUMA LONGA* L. RHIZOMA

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I. REGULATORY OVERVIEW

Member State	Herbal Medicinal Product Well-Established Use	Herbal Medicinal Product Traditional Use	Other Classification
Austria			
Belgium			
Bulgaria	-	-	
Cyprus			
Czech Republic	- **Combination medicinal product containing Curcumae longae rhizomatis pigmenta** 1969 *Preparation: Frangulae modinum 9 mg, Curcumae longae rhizomatis pigmenta 22.5 mg, Magnesii salicylas 100 mg, Eucalypti etheroleum 1 926 mg, Menthae piperitae etheroleum 3 600 mg, Levomentholum 9 mg/10 ml; *Since 1969 is the preparation on the market; *Pharmaceutical form: por gtt sol *Posology: for oral use, 5-10 drops three times daily; *Indications: cholelithiasis, chronic cholecystitis, dyspeptic disorders in chronic hepatitis and after surgery in biliary duct; *Contraindications: pregnancy (first trimester), lactation, in serious renal failure, acute inflammations in hepatobiliary tract, children under 12 years of age, children and adolescents under 17 years of age suffering with fever; *Special warnings: risk of Rey syndrome due to Magnesii salicylas content.	-	Pending registration: *Preparation: Fluid extract from *Curcuma longa* L., rhizoma extracted with mixture ethanol : water 1:1 (as dry residue) 100 mg/tbl, corresponding to 12.5 mg curcuminoides, calculated as curcumin; *Pharmaceutical form: por tbl nob; *Posology: for oral use, 1 to 2 tablets before meal, maximum daily dosage 8 tablets; *Indications (draft, not agreed yet): choleretic and cholagogue; treatment and prevention of functional digestive disorders of hepatic origin, hepatoprotective; *Contraindications (draft, not agreed yet): severe hepatic disorders, biliary obstruction, cholelithiasis, hypersensitivity to the components of the product.
Denmark	Kissinger tablets and pills, combination products (with 10 active substances) on market as laxative between 1956 and 1993.	-	Danish medicines Agency has no information regarding products marketed as food supplements.
Estonia	-	-	All products containing *Curcuma longa* are classified as non-medicinal products, probably classified as food supplements which requires registration at the Veterinary and Food Board.
Finland	-	-	
France			

Member State	Herbal Medicinal Product Well-Established Use	Herbal Medicinal Product Traditional Use	Other Classification
Germany	*Dry extract (13-25:1), ethanol 96% V/V; *for internal use, adults and adolescents over 12 years; *coated tablet: 3 x 1 containing 30 mg dry extract (max. 5 daily); hard capsule: 2 x 1 containing 81 mg dry extract; *Dyspeptic complaints, particularly based on functional affections of the biliary tract; *AR: GI complaints like feeling of fullness, heartburn, vomiting, diarrhoea; longer use may cause gastric pain; hypersensitivity reactions of the skin (frequency unknown); *I: no report of clinical interactions SPC: Animal tests and human *in vitro* tests indicate that there may be an influence of different phases of the CYP 450 system and the p-glycoprotein. Benefit/risk assessment has to be made carefully, if medicinal products which are metabolised by these systems, are taken concomitantly; *Authorised products on market, no pharamovigilance actions.	*Dry extract (13-25:1), ethanol 96% V/V; *for internal use, adults and adolescents over 12 years; *soft capsule: 3 x 1 containing 13.5 mg dry extract; *Traditional used to promote the digestion; *AR: GI complaints like feeling of fullness, heartburn, vomiting, diarrhoea; longer use may cause gastric pain; hypersensitivity reactions of the skin (frequency unknown); *Authorised products on market, no pharamovigilance actions.	
Greece			
Hungary			
Iceland			
Ireland	-	-	
Italy	-	-	
Latvia			
Liechtenstein			
Lithuania			
Luxemburg			
Malta			
The Netherlands	-	-	
Norway	-	-	One product a product containing curcuma and an amino acid, classified as food supplement, is widely used. 3 reports on pharmacovigilance associated with this product.

Member State	Herbal Medicinal Product Well-Established Use	Herbal Medicinal Product Traditional Use	Other Classification
Poland		Curcumae longae rhizoma extractum DER 1:5, extraction solvent: ethanol 70% v/v; *Indication: treatment of mild digestive disturbances and minor biliary dysfunction; *Posology: Adults: in digestive disturbances 10 ml once daily; as an adjuvant in biliary dysfunction 5 ml of the drug diluted with 60 ml water 3 times daily. Children from 12 years: in digestive disturbances 5 ml of the drug diluted with 60 ml water once daily; *AR: none known with exception hepersensitivity reactions *Authorised product on market	
Portugal	-	-	
Romania	-	-	
Slovakia	The herbal substance is only available in one authorised combination product. *Composition: Curcumae radicis pigmenta 0.0225 g, magnesii salicylas 0.18 g, menthae piperitae aetheroleum 3.6 g, eucalypti aetheroleum 1.926 g, frangulaemodinum 0.009 g; *indicated for cholelithiasis, chronic cholecystithis and dyspeptic disorders.	-	
Slovenia			
Spain	Dry hydroethanolic extract of dried rhizomes of *Curcuma longa* L. (5.5-6.5:1 ethanol 50% V/V) corresponding to 10-15 mg curcuminoids; *Posology: adults 1-2 tablets, 2 times a day, before meals. Adolescents over 12 years of age: 1 tablet, 2 times a day, before meals (tablets of 100 mg of dry extract as declared) *Indication: symptomatic treatment of mild digestive disturbances due to biliary disfunction * product is on the market, status: Publicitarias		
Sweden	-	-	Only one combination product is approved as natural remedy. Composition: *Curcuma longa, Cynara scolymus, Gentiana lutea*
United Kingdom	-	-	

I.1 INTRODUCTION

I.1.1 Description of the herbal substance(s), herbal preparation(s) or combinations thereof

Herbal substance

Curcumae longae rhizoma or turmeric, consists of the scalded and dried rhizomes of *Curcuma longa* L. *(C. domestica* Valeton) [102].

Other documented synonyms of *C. longa*: *C. aromatica* Salisbury and *Amomum curcuma* Jacq.) [18, 92]. Common names for *C. longa*: turmeric, curcuma.

Besides *C. longa* also *C. rotunda* is mentioned in some older references. Nowadays *C. rotunda* is considered to be a former trade name for the product containing the primary rhizomes (bulb or round turmeric) in distinction to the product consisting of the thinner and longer secondary rhizomes (longa-form), both originating from *C. domestica* L. [4, 46].

Other names: Curcuma, Indian saffron, Haridra (Sanskrit, Ayurvedic), Jianghuang (= yellow ginger in Chinese), Kyoo or Ukon (Japanese) [113].

The European Pharmacopoeia describes in the monograph for Curcumae xanthorrhizae rhizoma a TLC-test for *C. domestica* and its modifications for identifying *C. xanthorrhizae* [100].
The monographs of ESCOP and Commission E mention that the herbal substance contains not less than 2.5 resp. 3 percent dicinnamoylmethane derivates, calculated as curcumin, and not less than 2.5 resp. 3 percent volatile oil, both calculated on a dry–weight basis of the drug [108, 93].

Constituents
(see also Fig. 1)

Carbohydrates: 69.4% of total mass [2].

Curcuminoids: this is a mixture of curcumin (diferuloylmethane), monodexmethoxycurcumin and bisdesmethoxycurcumin [3-7]. Curcumin makes up approximately 90% of the curcuminoid content in turmeric [8].
The phenolic groups in the structure of curcumin explain the ability of curcumin to eliminate oxygen-derived free radicals. [9] The free radicals which can be eliminated by curcumin are hydroxyl radical [10], singlet oxygen [11], superoxide radical [12], nitrogen dioxide [13] and NO [14].
The curcumin content of the *Curcuma longa* rhizome varies from 0.6 to 5% of the dry mass [15]. The dry turmeric rhizomes contain 3-5% curcumin, the curcumin content of turmeric oleoresin is 40% [16].

Essential oil: 5.8% of total mass, constituents are: a-phellandrene 1%, sabinene 0.6%, cineol 1%, borneol 0.5%, zingiberene 25%, and sesquiterpenes 53% [2]. The mono- and sesquiterpenes include zingiberene, curcumene, α- and β-turmerone [3-7].

Mineral matter: 3.5% of total mass [2].

Moisture: 13.1% of total mass [2].

Polypeptides: [6, 7].

Protein: 6.3% of total mass [2].

Fatty oil: [17]

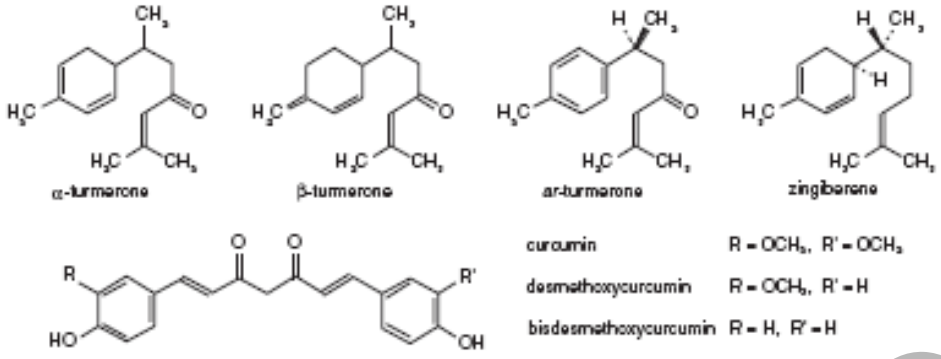

Fig. 1: Structures of main components of *Rhizoma Curcumae longae* [18].

Treatment of the herbal substance immediately after harvesting

According to some handbooks the plant material is processed before drying [92, 93,108]. Hager's Handbuch describes that after harvest, the rhizomes are cooked for a short time or heated with hot water [44-46]. The Indian and Japanese Pharmacopoeias also describe the 'curing', consisting of boiling and (sun) drying of the rhizomes as well as identification by different color reaction tests. The Chinese Pharmacopoeia mentions: collection of rhizomes, washing, boiling or steaming, cutting in thick slices, sun drying and separation from roots [117].
Max Wichtl's Herbal Drugs mentions that the yellowish brown color of the herbal substance is due to the steaming or scalding treatment after harvesting [4].

As pharmacological and (pre)clinical studies do not contain any data on the pretreatment of the plant material, and research data on the scalding effect are missing, the impact of the scalding treatment on the active compounds c.q. efficacy of *C. longa* preparations remains unclear. The scalding treatment is considered to be a traditional procedure mainly for food purposes.

Herbal preparations, specified for the individual final product

Powdered *Curcuma longa* rhizome [18, 93, 99, 108].
Ethanolic (80%) extract [19], [20-28]
Aqueous extract: [29, 30]
Ointment: 0.5% [31]
Tincture: (1:10) [18]
Paste: 15 g turmeric powder in 85 g petroleum jelly [32], or a mix of 1 part of turmeric powder with 4 parts of neem leaves (*Azadirachta indica*) [33].
Oil: 3-5.5% [34]
Oleoresin powder: 40% [35]
Essential oil: 70% (w/w) [35]

I.1.2 Information on period of medicinal use in the Community regarding the specified indication

Curcuma longa has been documented in the following handbooks:

Reference	Indication
"Lehrbuch der Phytotherapie" by R.F. Weiss (1974) [39]	Hauptbestandteil von Curry, das reizend auf die Schleimhäute des Magen wirkt und anregend auf der Gallenfunktion.
"Lexikon der Arzneipflanzen und Drogen" by K. Hiller (year unknown) [40]	Dyspeptische Beschwerden. In den Herkunftsgebieten bei entzündlichen und septischen Haut- sowie Augenerkrankungen.
"Pflanzliche Drogen" by W. Schneider (1974) [41]	Früher als Magenmittel und bei Gelbsucht, jetzt nur noch als Färbemittel.
"Drogenkunde" by H. Hoppe (1943) [42]	Mittel bei Leber- und Gallenleiden. Gegen Wechselfieber und Wassersucht. Magenmittel und Gewürz.
"Lehrbuch der biologischen Heilmittel" by G. Madaus (1938, reprint 1979) [43]	Gallen- und Gallentreibemittel, das auch bei Cholelithiasis. Cholangitis, Cholecystitis, dyspeptische Leberleidender und Ikterus angewandt wird.
"Hagers handbuch der pharmazeutischen praxis" by B. Reichert (1944, 1949) [44, 45]	Gegen Leberleiden, wirkt abführend [44]. Früher als Magenmittel und bei Gelbsucht, jetzt nur noch als Färbemittel [45].
"Hagers handbuch der pharmazeutischen praxis" by P.H. List (1973) [46]	Cholagogum und cholereticum, früher als Magenmittel und bei Gelbsucht.

Information on period of medicinal use outside the Community

Experience with *C. longa* in traditional medicinal systems outside the EU

In many Asian countries the use of turmeric as a food spice, colorant and medicine has a long tradition.

China, Japan, Korea, Vietnam, Nepal

Turmeric is used extensively in traditional Chinese medicine. It is official in the Pharmacopoeia of the People's Republic of China as well as in the Japanese Herbal Medicines Codex (JSHM, 1993) and is used in these countries and Korea for a range of indications including abdominal fullness, kidney pain, and amenorrhea. In China an aqueous decoction dosage form is ingested orally and applied topically [117].

India

Turmeric is used extensively in the Indian systems of medicine (Ayurvedha, Unani, and Siddha) and is official (Haridra) in the Ayurvedic Pharmacopoeia of India (API, 1989). In Ayurvedic medicine turmeric has a long history of use as an anti-inflammatory drug for arthritis. In both the Ayurvedha and Siddha systems of medicine, a turmeric paste is used topically to treat ulcers and scabies [117].

The Swami Prakashananda Ayurveda Research Centre lists as indications for turmeric: urticaria and skin allergy, viral hepatitis, inflammatory conditions of joints, sore throat and wounds [117].

I.2 NON-CLINICAL DATA

I.2.1 Pharmacology

I.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Documentation regarding the route of administration

Oral administration is the main route of administration for *Curcuma longa* preparations. *Curcuma longa* can also be used topically and via inhalation (Ayurvedic tradition).

Topical use of *C. longa*
Turmeric is applied topically for the treatment of acne, wounds, boils, bruises, blistering, ulcers, eczema, insect bites, parasitic infections, heamorrhages and skin diseases like herpes zoster and pemphigus [18, 37,113].
It is used in the form of a paste or ointment (mixture with oil or other substances), as a tincture or extract. However, no information could be found in literature on the composition of the products, the posology and the duration use.

Phytochemical research data on major components in *Curcuma longa*
Pozharitskaya *et al.* describe a HPTLC method to determine the total of curcuminoids and to determine curcumin, demethoxycurcumin and bisdemethoxycurcumin in *Curcuma longa*. A combination of HPTLC, with a diode array detector (DAD) and post chromatographic DPPH radical derivatisation was developed to separate and quantify the free-radical scavenging activity of individual compounds of *Curcuma longa* [47].

Sacchetti *et al.* characterized *Curcuma longa* essential oil using GC and GC-MS. Radical-scavenging and antioxidant properties were tested using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and luminol-photochemiluminescence (PLC) assay [48].

Pharmacodynamics

Anti-inflammation
Curcuminoids inhibit LOX, COX, phospholipases, leukotrienes, prostaglandins, thromboxane, nitric oxide [49, 50], elastase, hyaluronidase, collagenase, monocyte chemoattractant protein-1, interferon inducible protein, TNF and interleukin-12 [50].

Curcuminoids decrease prostaglandin formation and inhibit leukotriene biosynthesis via the lipoxygenase pathway [51].

Anti-depression
The effect of curcumin was investigated in a rat chronic mild stress (CMS) model. In comparison with normal rats, rats suffering the CMS procedure have a significant lower intake of sucrose, increased IL-6, TNF-α levels, CRF- and cortisol levels. Treatment with ethanolic extract increased the sucrose intake to normal control levels, reduced the CMS-induced increase in serum IL-6 and TNF-α levels and reduced the CRF levels in serum and medulla oblongata to lower than normal. It also lowered the cortisol levels in serum to normal levels [20].

A turmeric ethanolic extract was found to prevent chronic mild stress induced increase of serum IL-6, TNF-α, CRF- and cortisol levels [20].

Curcuma longa has antidepressant effects mediated through inhibition of monoamine oxidize A [61].

Curcuma longa ethanolic extract reversed the decrease in serotonin, noradrenalin and dopamine concentrations as well as the increase in serotonin turnover, cortisol levels and the in serum corticotrophin-releasing factor [21].

Curcumin increased brain-derived neurotropic factor in the frontal cortex and hippocampus [20].

Atherosclerosis

Curcumin mobilizes α-tocopherol from adipose tissue, this results in protection against oxidative damage produced during atherosclerosis development. Curcumin increases VLDL cholesterol transport in plasma, which results in increasing levels of α-tocopherol [52].

Cancer

Curcumin inhibits cell growth by inhibiting expression of basic fibroblast growth factor (FGF) and the angiogenesis factors vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF) [53].

Curcumin induces apoptosis of cancer cells [54] and it inhibits angiogenesis [55].

Curcumin blocks cyclosporine A-resistant phorbol myristate acetate + anti-CD28 pathway of T-cell proliferation [56].

Curcumin reduces the testicular damage caused by exposure to di-n-butylphthalate (DBP), by increase in Glutathion (GSH), testosterone levels and glucose-6-phosphate dehydrogenase (G6PD) activity and decrease in malondialdehyde (MDA) levels. These effects may be due to intrinsic antioxidative abilities of curcumin [57-59].

Dietary curcumin inhibits DMBA- and TPA-induced expression of ras-p21 and fos-p62 oncogenes [60].

Diabetes

A hexane extract (containing ar-turmerone), ethanolic extract (containing containing ar-turmerone, curcumin, demethoxycurcumin and bisdemethoxycurcumin) and ethanolic extract from the residue of the hexane extraction (containing curcumin, demethoxycurcumin and bisdemethoxycurcumin) were found to dose-dependently stimulate adipocyte differentiation. The results indicate that turmeric ethanolic extract containing both curcuminoids and sesquiterpenoids is more strongly hypoglycemic than either curcuminoids or sesquiterpenoids [22].

Hepatoprotective activity

Curcumin protects cells against lipid peroxidation induced by paracetamol. This may be due to the antioxidative effects of the phenolic groups of curcumin [74].

Curcumin was found to decrease serum aspartate transaminase and alkaline phosphatase activity, and free fatty acid, cholesterol and phospholipid levels [62].

The exact mechanism of action is still unclear.

Pharmacological activities of extracts of *Curcuma longa*

Antifungal, antibacterial, phytotoxic, cytotoxic and insecticidal activity

Khattak *et al.* studied the antifungal, antibacterial, phytotoxic, cytotoxic and insecticidal activity of an ethanolic extract of *Curcuma longa* (extract preparation not specified). The extract showed antifungal activity towards *Trichophyton longifusus* and *Microsporum canis* and weak antibacterial activity against *Staphylococcus aureus*. Toxic activity was observed against *Lemna minor*. The LD50 in a brine shrimp lethality bioassay *Curcuma longa* was 33 µg/ml. Curcuma showed no insecticidal activity [25].

Atherosclerosis

A high-cholesterol diet given to New Zealand White rabbits leads to development of atherosclerosis in the rabbits. Rabbits given a dietary supplement of a *Curcuma longa* extract in combination with a high-cholesterol diet showed a positive effect on the animals' antioxidant status compared to controls. Curcumin has shown to mobilize α-tocopherol from adipose tissue, thus protecting their body against oxidative damage produced during the development of atherosclerosis. Also more LDL cholesterol could be transported in plasma, increasing levels of α-tocopherol. Overall the fatty acids in the animals were less susceptible to oxidation in the vessel wall [52].

Diabetes

The effect of an ethanolic extract of turmeric on blood glucose levels in type 2 diabetic KK-A^y mice and stimulated human adipocyte differentiation was investigated by Kuroda *et al.* The extract was prepared by a two time extraction of powdered turmeric, with five volumes of ethanol. The extract was concentrated under reduced pressure to give 12.2 g of ethanolic extract. In the experiment on the human adipocytes a stimulation of adipocyte differentiation was observed. The activity of 5.0 µg/ml and 10.0 µg/ml ethanolic extract was more potent than that of 0.22 µg/ml and 0.44 µg/ml of troglitazone, which was therapeutically used as anti-diabetic and anti-inflammatory drug in humans, until it was withdrawn in 2000 for causing drug-induced hepatitis [23].

Nishiyama *et al*. studied the influence of three turmeric extracts on blood glucose levels in type 2 diabetic KK-A^y mice. The extracts used were an ethanolic extract, a hexanic extract and an ethanolic extract from the residue of the hexane extraction. The ethanolic extract and hexanic extract were obtained from powdered *Curcuma longa* by extracting twice with five volumes of ethanol or hexane and filtration and evaporation of the solvent. The ethanolic extract from the residue of the hexane extraction was obtained using the same method. To determine the mechanism of action the extracts were tested for adipocyte differentiation. No difference in bodyweight were observed between treated and control animals. The ethanolic extract stimulated adipocyte differentiation dose-dependently. The hexanic extract and the ethanolic extract from the residue of the hexane extraction showed similar effects but at higher concentration as the ethanolic extract [22].

Hepatotoxicity

Soni *et al.* investigated the preventive effect of an aqueous extract of turmeric on liver damage in ducklings induced by aflatoxin. The extract was prepared by boiling 1 g of turmeric powder in 100 ml water. After concentration it was made up to 10 ml. The aqueous turmeric extract (10 mg/ml) inhibited toxin production by 99%. An alcoholic extract of turmeric showed inhibition as well, except on a much lower level. Turmeric and curcumin treatment showed almost complete reversal of fatty changes and necrosis induced by aflatoxin [29].

Mutagenicity

Azuine *et al.* investigated the protective effect of an aqueous turmeric extract on chemically induced mutagenicity in *Salmonella typhimurium* strains and clastogenicity in mammalian bone marrow in female Swiss mice. The anticarcinogenic effects were assessed in the benzo(a)pyrene-

induced forestomach neoplasia model. The extract was prepared adding 5 ml boiling distilled water to 50 mg turmeric powder. This was mixed at room temperature for 20 minutes by vortexing at 150 rpm (Orbit Shaker, Lab Line). The supernatant was collected and lyophilized. Aqueous turmeric extract exhibited antimutagenic activity against direct acting mutagens. The turmeric extract also inhibited the mutagenicity of benzo(a)pyrene in *Salmonella typhimurium* strains. Treatment with the aqueous tumeric extract inhibited the development of forestomach tumors induced by benzo(a)pyrene significantly. These findings were all dose-dependent [30].

Myocardial apoptosis

The effect of *Curcuma longa* on myocardial apoptosis in experimentally induced myocardial ischemic-reperfusion injury was investigated by Mohanty *et al.* Winstar rats were fed 100 mg/kg *Curcuma longa* once a day, for one month. *Curcuma longa* treated rats demonstrated significant anti-apoptotic property, which might contributed to the observed preservation in cardioprotective effects and cardiac function [63].

Pregnancy/neonates

Singh *et al.* followed dams and their suckling neonates to determine the modulatory influence of turmeric and curcumin on hepatic biotransformation system enzymes. Turmeric and curcumin induced a significant increase in hepatic levels of glutathione S-transferase (GST) and sulfhydryl (SH) levels. Cytochrome b5 and cytochrome P450 levels were significantly elevated as well. This indicates that turmeric and/or curcumin metabolites can be transferred through lactation [64].

Ulcers

Kim *et al.* investigated the protective effect of *Curcuma longa* ethanolic extract against gastric ulcers by blocking H_2 histamine receptors (H_2R) of male Sprague-Dawley (pylorus-ligated) rats. The extract was prepared by fluxing 100 g *Curcuma longa* with 80% ethanol. This was shaken at room temperature for 24 hours, this was performed twice. After extraction, the fluid was concentrated with rotary vacuum evaporator (EYELA, Japan). The ethanolic extract was dissolved in 100 ml H_2O and fractionated with organic solvents, *n*butanol and ethyl acetate. For *in vitro* tests the dried material was resuspended in DMSO, for *in vivo* tests the dried material was resuspended in saline. The effect of *Curcuma longa* extract was compared to the effects of ranitidine. Curcuma was found to protect the gastric mucosal layer as effective as ranitidine. Orally administerd ethanolic extract (unknown amount) inhibited gastric acid, gastric juice secretion and ulcer formation comparable to the effects of ranitidine. Curcuma also suppressed histamine-induced cAMP production, caused by direct inhibition of H_2R, curcumin however had no effect on cAMP formation [24].

Rafatullah *et al.* investigated the antiulcer activity of an ethanolic extract of turmeric in inbred Winstar albino rats. The extract tested was a dried 96% ethanol extract. Administration of turmeric extract led to a significant decrease in ulcer index and acidity of stomach contents. Pretreatment with the turmeric extract reduced the intensity of ulceration induced by indomethacin or reserpine administration. Hypothermic-restraint stress reduction of gastric wall mucus, was inhibited by turmeric extract treatment. Treatment with turmeric extract reduced the severity of lesions induced by various necrotizing agents. Turmeric extract reduced the decrease in gastric mucosal non-protein sulfhydryl groups induced by administration of 80% ethanol [19].

Wound healing

The woundhealing effects of *Curcuma longa* paste were studied in rabbits. The *Curcuma longa* treated group showed a significant higher mean value for contraction of the wound compared to controls. Furthermore the wounds showed less inflammation and an increasing trend in the formation of collagen [32].

Pharmacological activities of combination preparations

No data available.

Pharmacological activities of curcumin

Antiplatelet property

The antiplatelet property of ar-turmerone was investigated. Ar-turmerone showed strong inhibitory activity against platelet aggregation mediated by collagen and arachidonic acid. At higher concentrations curcumin showed the same effect. However, only a weak or no inhibitory effect was observed against PAF or thrombin activated platelets. The other components in the ethanolic extract showed no inhibitory effects [27].

Comparison between ar-turmerone and aspirin showed that ar-turmeron inhibited platelet aggregation induced by collagen more effective and aspirin inhibited platelet aggregation induced by arachidonic acid 1.2 times more effective [27].

Cancer

Curcumin was found to inhibit *in vitro* tumor cell growth by inhibiting expression of basic fibroblast growth factor (FGF) in breast cancer-cell cultures and the angiogenesis factors vascular endothelial growth factor (VEGF) and basic fibroblast growth factors (b-FGF) [53].

Curcumin was effective in squamous-cell carcinoma model. The study of Li ***et al.*** showed a reduced occurrence of chemically induced tumors by 50 percent [65].

Curcumin blocks cyclosporine A-resistant phorbol myristate acetate + anti-CD28 pathway of T-cell proliferation and thus may be a potential adjuvant immunosuppressive agent for the treatment of cancer [56].

Farombi ***et al.*** carried out a study to determine the ameliorative effects of curcumin and kolaviron (a biflavonoid from the seeds of *Garcinia kola*) on the di-n-butylphthalate (DBP)-induced testicular damage in rats [66]. The level of glutathione (GSH), the glucose-6-phosphate dehydrogenase (G6PD) activity and the decreased testosterone levels were significantly increased [66]. The increased levels of malondialdehyde (MDA) were decreased, which is in agreement with Ishihara *et al.* [66, 67]. This may be due to the intrinsic antioxidative abilities to combat oxidative damage induced by DBP [66].

Mice exposed to human prostate cancer cells were treated with curcumin. The curcumin-treated animals showed a decrease in microvessel density and cell proliferation and an increase in apoptosis compared to controls [55, 68].

Incubation of endothelial cells from bovine aorta with curcumin (in a concentration range of 5-15 μM) showed induction of heme oxygenase expression. Heme oxygenase is an enzyme that reacts to oxidative stress, by producing the antioxidant biliverdin, and it enhances resistance tot oxidative damage to cells [73].

The efficacy of curcumin or turmeric extract in reducing chemically-induced tumours in male Swiss albino mice was studied by Soudamini and Kuttan. The extract was prepared by extraction of 5 g of powdered turmeric with 100 ml acetone/methanol (45:55). The extract was filtered using filter paper. 40 mg of curcumin was dissolved in 5 ml acetone/methanol (45:55). DMBA was used to induce tumors. Single application of curcumin or turmeric extract failed to inhibit papilloma formation. A small, non significant, reduction in papilloma formation was seen in the turmeric extract treated group, compared to the control group. Application of both curcumin and turmeric

extract during carcinogenesis and promotion resulted in less papilloma production, compared to controls. This indicates that both curcumin and turmeric extract produce their best effects during tumour promotion [70].

The effect of dietary curcumin (0.2% and 1.0%) on 7,12-dimethylbenz(a)anthracene (DMBA) and 12,0-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumor formation in Swiss albino mice was investigated by Limtrakul *et al.* They found a significant lower number of papillomas in the curcumin treated group compared to the control group. The enhanced expression of ras-p21 and fos-p62 oncogenes were decreased dose dependently in the curcumin treated group [57].

Antioxidant properties

Curcumin is not an efficient hydroxyl radical scavenger or quencher of superoxide [71].

Mutagens

Nagabhushan *et al.* tested curcumin against tobacco products and several environmental mutagens in a Salmonella/microsome test with or without Aroclor 1254-induced rat liver homogenate (S-9 mix), in order to determine the difference between mutagens which require metabolic activation and those who do not. Curcumin inhibited the mutagenicity of bidi smoke condensate, cigarette smoke condensate and masheri (a tobacco product) and tobacco extracts in a dose-dependant manner. Curcumin is only antimutagenic against mutagens which require metabolic activation [72].

Diabetes

Arbiser and Okamoto *et al.* reported that curcumin reduces the destructive angiogenesis associated with diabetic retinopathy [58, 59].

Hepatoprotective activity

Tacrine is known for its T-cell destructive activity and hepatotoxicity. In a study with cultures of human hepatocytes, which had been destroyed by tacrine, curcumin showed to be nearly ten times more effective than the regular treatment, ascorbic acid [60]. However, a study on carbon tetrachloridetoxicity in mice, performed in 1996, showed no protective effects due to curcumin administration at dosages of 200 mg per kg [69].

Donatus *et al.* investigated the effect of curcumin on the cytotoxic effect of paracetamol in rat hepatocytes. Curcumin showed no protective effect against paracetamol induced GSH-depletion in hepatocytes of 3-methyl-cholanthrene pretreated rats. Curcumin in a concentration of 5×10^{-5}, 5×10^{-4} and 5×10^{-3} M protected the cells against lipid peroxidation induced by paracetamol. This effect may be due to the two phenolic groups of curcumin, which give it strong anti-oxidant effects [74].

The effect of curcumin on alcohol induced hepatotoxicity in alcoholic rats were studied by Rajakrishnan *et al.* Compared to the control group curcumin administration resulted in a decrease of serum aspartate transaminase and alkaline phosphatase activity. The levels of serum free fatty acids, cholesterol and phospholipids decreased as well [62].

Stress

Xu *et al.* investigated the effect of orally administered curcumin on behavior in a chronic stress model of depression in rats. The molecular targets of curcumin were studied as well. The antidepressant imipramine was used as a positive control. Chronic curcumin administration (at 10 mg/kg) showed similar effects as imipramine. These findings suggest that the effects of chronic administration of curcumin on the behavior of chronic stressed rats may be related to the modulating effects of the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, through selective increase in brain-derived neurotropic factor in the frontal cortex and the hippocampus of the rats [20].

Blood lipids

In a small study with 10 healthy volunteers it was observed that oral intake of 500 mg/d curcumin for 7 days resulted in a significant decrease in the level of serum lipid peroxides (33%) and increase in HDL cholesterol (29%) and a decrease in level of total serum cholesterol (12%) [116].

Toxicity

A study in which monkeys were fed 0.8 mg/kg of curcumin a day for 90 days and rats 1.8 mg/kg a day for 90 days showed no adverse effects [75].

I.2.1.2 Overall conclusions on pharmacology

Results from *in vitro* and *in vivo* studies with whole extracts of *Curcuma longa*, and isolated compounds, support the traditional use of *Curcuma longa*.

I.2.2 Pharmacokinetics

I.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Little is known about the pharmacokinetic pathway of curcumin [76]. Doses up to 5 μg/ml of curcumin added to microsome- and hepatocyte suspensions disappeared within 30 minutes [77].

In rats, 40-75% of orally administered curcumin is excreted in the feces. Blood levels of less than 5 μg/ml indicate poor absorption from the gut [77, 78].

I.2.2.2 Overall conclusions on pharmacokinetics

Available data suggests that curcumin is poorly absorbed from the gut, rapidly metabolized and excreted in feces.

I.2.3 Toxicology

I.2.3.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Donatus *et al.* found curcumin to be moderate cytotoxic. At a concentration of 5×10^{-3} curcumin slightly increased LDH-leakage from rat hepatocytes. This increase was accompanied by an increase in GSH-depletion, which can result in increased susceptibility to cytotoxicity [74].

Liver toxicity has been reported, but most of these incidents involved large dietary doses (turmeric 0.2%, 1.0%, 5.0%) or turmeric ethanolic extract 0.05%, 0.25%) given to mice or rats [26].

No mutagenic effects were found in the Ames tests for curcumin and turmeric extracts (information on preparation could not be found) [79].

A single feeding of 30% turmeric diet to rats produced no toxic effects [75].

No effects on chromosomal damage, pregnancy rate, number of dead embryos, total implants and mutagenic effects were observed in mice fed with turmeric (0.5%) or curcumin (0.015%) [80].

In mice fed for 14 days with a diet containing 1% and 5% turmeric hepatotoxicity was observed [26, 81]. Rats fed with turmeric 1% for the same period showed no adverse affect. The rats fed

turmeric at a dose of 5% of their diet for a period of 90 days showed a reduction in body weight gain and hepatotoxicity [26].

I.2.3.2 Overall conclusions on toxicology

Neither *Curcuma longa* nor curcumin appear to be mutagenic, or toxic for embryos or implants. However, with a high (dietary) intake hepatotoxicity was observed.

I.3 CLINICAL DATA

I.3.1 Clinical pharmacology

I.3.1.1 Pharmacodynamics

No published data available.

I.3.1.2 Pharmacokinetics

In humans the estimated bioavailability of curcumin after oral administration is 65%. Cytochrome P 450 isoenzyme 1A1 is inhibited by curcumin and is metabolized by glucuronidation [28].

In a phase I clinical study subjects had average peak serum concentrations of 0.5, 0.6 and 2 μM after taking 4-, 6- or 8-g doses of curcumin. Urinary excretion of curcumin was not detectable [89].

I.3.2 Clinical Efficacy / Longstanding use and experience

Medicinal uses of *Curcuma longa* have been reported in several European handbooks:

- septic skin disease [40, 43]
- liver disease [40, 42, 44]
- anti-tumor [40]
- anti-mutagenic [40]
- dyspepsia [43, 45]
- parasitic infections [43]
- jaundice [45]
- muscle relaxant [46]

I.3.2.1 Posology and duration of use

Turmeric is taken orally or applied on the skin. It is used as a powder (e.g. in capsules or to dissolve in fluid), as an ethanolic or aqueous extract, as paste, ointment and as oil [15, 19, 30-33, 36, 64, 79, 80, 90-94].

There are no dose-response studies available. The following posology is described in literature:
1.5-3 g of powdered turmeric root is usually recommended for use against dyspeptic/digestive disorders [18, 92, 93,108].
Turmeric is taken in doses of 5-30 g daily for acute problems or 3-10 g daily for chronic problems in inflammatory conditions [95].

According to the Professional's Handbook of CAM, a three times daily dosage of 400-600 mg of curcumin or 8-60 g of fresh turmeric root is recommended in arthritis [97].

For chemopreventive use, the recommended daily dose of curcumin is approximately 500 mg per day [96]. This corresponds to a daily intake of 170 g of powdered turmeric of raw rhizome, when assuming that the rhizome contains an average quantity of curcumin of 3% [15].

Other dosage recommendations are:
- powdered plant material: 1.5-3.0 g daily [18, 93, 99, 100, 108]
- oral infusion: 0.5-1 g three times a day [4, 18]
- tincture (1:10): 0.5-1 ml three times per day [18]

In Germany, there are two preparations with *C. longa* dry extract (DER 13-25:1; ethanol 96%) on the market: As a 'WEU' product: coated tablet/hard capsule with posology 3 x 30 mg/2 x 81 mg daily for dyspeptic complaints; as a 'Traditional Use' product: soft capsule with posology 3 x 13.5 mg daily to promote the digestion.
In Poland, an oral liquid with turmeric extractum (DER 1:5, ethanol 70%) is authorized as medicinal product for traditional use for the symptomatic treatment of mild digestive disturbances and minor biliary dysfunction (posology 10 ml once daily or 5 ml in 60 ml water 3 times daily, respectively).
In Spain there is one preparation containing *C. longa* dry extract (DER 5.5-6.5:1 , ethanol 50%) authorized as a 'WEU' medicinal product (posology 2 x 1-2 tablets of 100 mg) for traditional use for the symptomatic treatment of mild digestive disturbances due to biliary dysfunction. See also Regulatory Overview.

For topical application no clear indications for posology could be found in literature.

Duration of use

Information on the recommended duration of use could not be found. As clinical safety studies are lacking, it is proposed to limit the duration of use to two weeks.

I.3.2.2 Clinical studies (case studies and clinical trials)

Dyspepsia
In a randomized, double-blind, placebo-controlled multicentre study of Thamlikitkul *et al*. (1989), 106 patients with dyspeptic complaints (such as abdominal pain, epigastric discomfort, flatulence or belching) were treated daily for 7 days with 2 g of turmeric (n=38), a herbal combination including cascara and nux vomica and ginger (n=30) or placebo (n=38). At the end of the study 87% patients in the turmeric group, 83% in the herbal extract mixture group and 53% in the placebo group reported a notable improvement. The difference between turmeric and placebo was significant and clinically relevant (p=0.003) [115].

Irritable bowel syndrome
A partially blinded trail was performed with 207 volunteers with self-reported irritable bowel syndrome. Patients were divided in 2 groups: one was treated with 72 mg (1 tablet) and the other with 144 mg (2 tablets) of a standardized extract of tumeric extract (Cynara Lichtwer from Pharma UK), No data were provided on the extraction solvent and the compound(s) used for standardization. Intake of tumeric resulted in a significant reductions (compared to baseline) of IBS prevalence, 53% and 60% in the one- and two-tablet groups respectively ($p<0.001$)) as well as in a significant decrease in pain and discomfort (22% and 25% in the one- and two-tablet group respectively). Also a significant improvement of quality of life, improvement of IBS and increased normal bowel pattern was observed [49]. However, no significant difference was observed between the two groups. There was no placebo group in the trial, According to the authors there is "*little doubt that the placebo effect contributed to the improvement seen*." [49].

Mutagens

In a clinical trial performed in 1992 the effects of turmeric administration on urinary excretion of mutagens (in 16 chronic smokers and 6 non-smokers) were investigated. Turmeric was administered at a dose of 1.5 g/day for 30 days. The non-smokers had low excretion of mutagens at baseline, compared to smokers. Intake of turmeric by the smokers resulted in a significant decrease in urinary mutagen excretion, compared with baseline [82].

Peptic ulcers

The effect of turmeric on peptic ulcers was studied in 2001 in an uncontrolled trial performed in Thailand. A group of 25 subjects received five doses of 600 mg of turmeric a day, for 12 weeks. After 12 weeks 19 subjects had no ulcers [83].

Cancerous lesions

In the study of Kuttan *et al*. (1987) an ethanol extract of turmeric ("Curcuma longa") as well as an ointment of curcumin were found to relieve the symptoms associated with external cancerous lesions. Reduction in smell was noted in 90% of the cases and reduction in itching in almost all cases. Dry lesions were observed in 70% of the cases, and a small number of patients (10%) had a reduction in lesion size and pain. In many patients the effect continued for several months. An adverse reaction was noticed in only one of the 62 patients evaluated [31].

For an overview of clinical studies with *C. longa* preparations, combination preparations and curcumine, see the tables below.

Overview of clinical studies with *C. longa* preparations.

Author, date	Study type and duration	Patients	Treatment, daily dosage	Parameters	Results	Conclusion/Discussion
Bundy *et al*., 2004 [49]	Pilot study, partially blinded, R[1] two-doses, 8 weeks	207 volunteers selected with Rome II criteria	1 or 2 tablets of 72 mg standardised turmeric extract (no details)	IBS prevalence, symptom related Q of Life and self-reported effectiveness	IBS prevalence reduced in both groups, abdominal pain/discomfort score reduced sign. by 22% and 25% in 1 tablet and 2 tablet groups resp. , improvement in symptoms, no significant differences between groups.	No data on the extraction solvent and the compound(s) used for standardization. No placebo group in the trial. According to the authors there is "little doubt that the placebo effect contributed to the improvement seen.."
Häringer, 2004 [113]	MC[1] Anwendungsbeobachtung (AWB) 12 weeks	221 patients with functional dyspepsy (Rome II criteria)	2.8 g (2 tablets of 81 mg dry extract (13-25:1))	Nepean Dyspepsy Index (15 symptoms); fat metabolism	154 patients finished trial; after 6 weeks 33%, after 12 weeks 54% less symptoms.	No Placebo, subjective assessments; Methodological short comings
Kammerer & Fintelmann, 2001 [114]	31 days	440 patients with dyspepsy, functional disorders of bileducts	2.8 g (2 tablets of 81 mg dry extract (13-25:1)) for 28 days	9 symptoms	64% reduction of symptoms; 36% of patients symptom free; 56% continued treatment; 7% ended prematurely, for no relief.	No Placebo, subjective assessments; Methodological short comings
Kuttan *et al*., 1987 [31]	?	62 patients	Ethanolic extract of *C. longa* as well as ointment of curcumin	Smell, itching, lesion size	Reduction in smell (90% of cases), Reduction of itching (all cases), dry lesions (70% of cases), reduction in lesion size and pain (10% of cases)	No details on study type, formulation and application
Polasa *et al*., 1992 [82]	Uncontrolled, 30 days	22 normal men (16 chronic smokers, 6 non-smokers), India	1.5 g (2 tablets of 750 mg turmeric)	Urine testing after 0,15, 30 days, biochemical parameters, mutagenicity assay	Reduction of urinary excretion of mutagens in smokers	Turmeric administration may reduce the genotoxicity of tobacco mutagens. Clinical relevance is not clear.

[1] R = randomised
P = placebo-controlled
DB = double blind
MC = multi centre
CO = cross-over

Prucksunand *et al*., 2001 [83]	Phase II, uncontrolled 4 weeks	45 patients with symptoms indicating peptic ulcer, 16-60 years	3 g (2 capsules 300 mg turmeric five times daily)	Symptoms pain and discomfort, blood chemistry and hematology	Abdominal pain and discomfort subsided in 1st and 2nd week, no significant changes in blood chemistry and hematology, liver and renal functions	Methodological shortcomings (e.g. baseline, not all patients endoscoped)
Thamlikitkul *et al*., 1989 [115]	MC R P DB[1] 3-arm, 7 days	116 patients with dyspepsia (acid / flatulent /atonic) C. domestica: 39 P: 41 'Flatulence': 36	2 g powder of dried turmeric rhizome (2 x 250 mg capsules 4 times) or 'Flatulence' (traditional treatment)	Symptoms, adverse events, compliance & acceptance	Response: P: 53%, F: 83%, C: 87% In all groups mild adverse events	This s the only placebo controlled trial performed with *Curcuma longa*. However the article contains very little information on the medical protocol used. No information on the blinding of the clinical assessors. No difference was observed with regard in the patient's satisfaction. Comparator is not a standard treatment

Overview of clinical studies with *C. longa* containing combination preparations.

Author, date	**Study type and duration**	**Patients**	**Treatment, daily dosage**	**Parameters**	**Results**	**Conclusion/Discussion**
Charles and Charles, 1992 [33]	Pilot study	814 patients with scabies	Ayurvedic formulation of turmeric and *Azadirachta indica* (Neem) as paste (topical use)	Number, size and type of lesions	In 97% of cases cure within 3-15 days, no adverse effects	Efficacy was not assessed because efficacy of a combination can not be extrapolated to mono-preparations
Kulkarni *et al*., 1991 [38]	R DB P CO[1], 2 x 3 months	42 patients with osteoarthritis	3 x 2 capsules of 650 mg of *C. longa* containing Ayurvedic herbomineral formulation (corresponding to 50 mg turmeric each)	Pain and disability score	Significant drop in severity of pain and disability score, mild side-effects (nausea, dermatitis, pain in abdomen)	Efficacy was not assessed because efficacy of a combination can not be extrapolated to mono-preparations

Overview of clinical studies with curcumin.

Author, date	Study type and duration	Patients	Treatment, daily dosage	Parameters	Results	Conclusion/Discussion
Rasyid, Lelo 1999 [91]	R DB P CO[1]	12 healthy volunteers	20 mg curcumin single dose	Contraction effect on human gall-bladder	Significant reduction of gall bladder volume after 0.5 h-2.0 h (12-29%, resp.), no side-effects	Further dose-responding studies needed to find optimal dose of curcumin to induce 50% contraction
Soni, Kuttan 1992 [29]	Uncontrolled, 7 days	10 healthy volunteers	500 mg curcumin	Serum level of cholesterol and lipid peroxides	Decrease serum lipid peroxides (33%), increase in HDL cholesterol (29%), decrease in total serum cholesterol (12%)	Follow-up study needed of curcumin as preventive substance against arterial diseases

[1] R = randomised
P = placebo-controlled
DB = double blind
MC = multi centre
CO = cross-over

Pharmacological activities of combination preparations

Osteoarthritis

Kulkarin *et al.* investigated the effect of a herbomineral formulation (a combination of turmeric with Ashwagandha (*Withania somnifera*), Sallai Guggul (*Boswellia serrata*) and Jasad Bhasma (zinc) based on Ayurvedic medicine) on osteoarthritis. Short term effects of the herbomineral formulation were significant alterations in the severity of pain and disability. Other changes like less morning stiffness, better grip strength and joint score, however, were not significant [38].

Scabies

In a pilot study with 814 patients, a combination of turmeric and neem in the form of a topical paste was found to effective in treating scabies. 97% of the patients were cured within 3-15 days of treatment [33].

Pharmacological activities of curcumin

Arthritis

The efficacy of a combination of curcumin and frankincense was studied in a placebo controlled trail in 90 patients with osteoarthritis. Patients were treated for 32 weeks. After 16 weeks and 32 weeks of treatment a significant reduction in pain ($P<0.05$) was observed. The treatment resulted in a significant improvement in WOMAC (Western Ontario McMaster University OA Index, Likert scale, version 3.0) scores ($P<0.01$) [84].

Deodhar *et al.* performed a double-blind clinical trial in which curcumin 1200 mg/day was compared with phenylbutazone 300 mg/day in 18 patients with rheumatoid arthritis. Both curcumin and phenylbutazone improved walking time, morning stiffness, and swelling, but only phenylbutazone improved 'fatigue time'. Both drugs were assessed as producing an overall improvement over baseline. However, the patients only rated phenylbutazone as better for controlling symptoms, compared with baseline [85].

Biliary effects

In animal models an increase of the bile flow and the bile excretion were observed after intravenous administration of up to 500 mg/kg of an aqueous alcohol turmeric extract [109-112].

Gall-bladder function

In a randomised double-blind crossover study in 12 healthy volunteers ultrasonic examination revealed that the contraction of the human gall-bladder is stimulated by a single oral dose of 20 mg of curcumin [91].

Cancer

In an open clinical trial a curcumin 0.5% ointment was tested in 62 patients with skin and mucous membrane cancers. The ointment was applied three times daily for a minimum of four weeks. A total of 68% of the patients responded (reduction in exudates 70%, lesion smell 90%, and pain 50%) [31].

Chronic anterior uveitis

In an open clinical trial, curcumin was administered in an oral dose of 375 mg three times daily for 12 weeks to 53 patients with chronic anterior uveitis. Symptoms improved after 12 weeks of therapy in about 90% of the patients who completed the trial. 47% had repeated episodes of anterior uveitis in a three-year follow-up [36].

Inflammation

Human trials have demonstrated that a dose of 400 mg of curcumin, three times per day, can reduce postoperative inflammation as effectively as the NSAID phenylbutazone [87].

Pancreatitis

Durgaprasad *et al.* investigated the effect of oral administration of curcumin with piperine in 20 patients with tropical pancreatitis on pain and markers of oxidative stress. The patients received 500 mg of curcumin in combination with 5 mg of piperine or placebo for a period of 6 weeks. A significant reduction in erythrocyte MDA levels was observed, as well as a significant increase in GSH levels compared to placebo. No effect was observed on the pain. These effects indicate that curcumin in combination with piperine reverses lipid peroxidation in patients with tropical pancreatitis [88].

I.3.2.3 Clinical studies in special populations (e.g. elderly and children)

No published data available.

I.3.2.4 Overall conclusions on (clinical) efficacy / traditional medicinal use

The use of *Curcuma longa* against dyspepsia, skin and liver diseases is well documented in a number of handbooks.

The traditional use is supported by a substantial amount of data on the pharmacological effects of curcuma root, curcuma extract and curcumin. However clinical data is very limited. Only 5 trials have been published for curcuma (extract), of which one is placebo controlled and relevant as to the mentioned indications.

The study of Thamlikitkul *et al*. performed in 1989, is the only placebo controlled trial performed with *Curcuma longa*. However the article contains very little information on the medical protocol used. For example according to the title of the article the trial was double-blinded but the article does not contain information on the blinding of the clinical assessors. The comparison to placebo treatment with curcuma resulted in a statistically significant improvement of dyspeptic symptoms, yet no difference was observed with regard to the patient's satisfaction.

Several trials were performed with curcumin. Not withstanding the fact that it is questionable if the activity of an isolated constituent can be used to justify the efficacy of a herbal medicinal product, the studies performed with curcumin have limited value for the monograph because they were performed with either a very high dose or with combination products. Furthermore the trials were conducted on diseases for which curcuma has no well established use in the EU. In conclusion the available data is not sufficient to support a "well established use" indication for curcuma.

I.3.3 Clinical Safety / Pharmacovigilance

I.3.3.1 Patient exposure

No data available.

I.3.3.2 Adverse effects

The Food and Drug Administration classifies turmeric as a substance Generally Recognized as Safe [50].

No major side effects have been reported in the clinical studies [3, 49, 91].

No side-effects were reported in patients with rheumatoid arthritis treated with 1200 mg/day of curcumin for two weeks [85].

In a phase I trial with 25 subjects, who had various high-risk cancerous conditions, no toxic reactions were observed. The subjects received up to 8 g of curcumin a day for 3 months [89].

In a clinical study in patients with irritable bowel syndrome dry mouth and flatulence was reported by approximately 25% of the patients [49]. In another study two of 19 patients treated with 2500 mg of curcumin per day, complained of gastric irritation. No other adverse effects were reported [101]. In the study of Thamlikitkul mild side-effects as nausea, diarrhoea, headache, tiredness and sleepiness have been reported in the turmeric group (2 g/day) as well as in the other groups (placebo and comparitive herbal combination) [115].

Rare cases of allergic contact dermatitis have been reported [102, 103]. In an 18-month study on the topical use of curcumin to treat skin and mucous membrane cancers, scalp itching was observed in 1 patient of 62 patients, [31]. Patch testing led to allergic reactions (not further classified) in persons who were regularly exposed to the substance or who already had dermatitis of the finger tips. Few allergic reactions (skin rash) occurred to people not previously exposed to curcumin [104].

Pharmacovigilance problems have been reported for a product containing curcuma and a amino acid. Further study revealed that the observed liver toxicity was not due to curcuma.

Assessors comment:
The inhibitory effects of curcuminoids on COXs correlates with the ulcerogenic activity in observed rats: ulcus index 8-10 times higher than control. These findings suggest that curcuma extracts should not be used by patients with duodenal/gastric ulcers. However in a phase II study, a gastro protective action was observed in patients with peptic ulcer disease after oral intake of 600 mg curcumin 5 times daily [Prucksunand *et al.*, 2001]. Therefore no contraindication for duodenal/gastric ulcers was included in the monograph.

I.3.3.3 Serious adverse events and deaths

No data available.

I.3.3.4 Laboratory findings

No data available.

I.3.3.5 Safety in special populations and situations

No data available.

I.3.3.5.1 Intrinsic (including elderly and children) / extrinsic factors

No data available.

I.3.3.5.2 Drug interactions

Turmeric may interact with NSAIDs, antiplatelet agents or antihyperlipidemics [94], although there have been no reports in humans [97].

The antiplatelet activity has only been observed in animal studies. Clinical data is lacking [97]. Therefore this interaction is not included in the monograph.

Fetrow suggested that curcumin could decrease the effect of immunosuppressants, although no supporting data was provided [97].

Reports on interaction between warfarin and turmeric are mainly based on *in vitro* data, animal studies or individual case reports. More studies are needed to confirm and assess the clinical significance of this potential interaction [105].

Several studies reported interactions between curcumin and other phytochemicals. When healthy human subjects took a 2 g dose of curcumin in combination with 20 mg of piperine, extracted from black pepper, the bioavailability of curcumin increased twenty-fold compared to subjects who took only 2 g of curcumin [106].

Green tea enhances the effect of curcumin. In Swiss mice and Syrian golden hamsters tumor models the combination of catechin and turmeric was more effective than the individual components [107]. Recently it has been suggested that curcumin and green tea extract have synergistic effect in reducing oral squamous-cell carcinomas in hamsters [65].

I.3.3.5.3 *Use in pregnancy and lactation*

There are no reports on the use of curcumin during pregnancy and lactaction [15, 92].

Singh et al. observed pharmacological effects in dams as well as their suckling neonates when turmeric and/or curcumin was administrated to the dams. The results indicate that turmeric and/or curcumin metabolites (not specifically mentioned) can be transferred through lactation [64]. Hence the use of curcumin during breast-feeding is not recommended [92].

I.3.3.5.4 *Overdose*

No toxic effects were observed after three months oral intake of 8,000 mg or 2.2 g of turmeric (equivalent to 180 mg of curcumin) a day for four months [89, 96].

I.3.3.5.5 Drug abuse

No data available.

I.3.3.5.6 Withdrawal and rebound

No data available.

I.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

No data available.

I.3.3.5.8 Contra-indications

Because curcumin was found to stimulate the gall bladder, the use of curcumin or turmeric is contraindicated in patients with obstruction of the biliary tract [18, 91, 92, 108]. This contraindication is also mentioned in the WHO monograph and in the Kommisson E monograph [18, 92].

I.3.3.6 Overall conclusions on clinical safety

No serious side effects have been reported up to now. Furthermore the chemical composition of *Curcuma longa* does not give any reason for concerns regarding safety.
Potential interactions between *Curcuma longa* and NSAIDs, antiplatelet agents, antihyper-lipidemics and immunosuppressants have been reported, but this has not clinically been proven The

use of *Curcuma longa* in pregnant women and during lactation is not recommended while there are indications that metabolites of *Curcuma longa* can be transferred through lactation.

I.4 OVERALL CONCLUSIONS

Curcuma longa has been used in Europe for a long time, mainly against dyspepsia, skin and liver diseases and infections. However, the available data is not sufficient to support a "well established use" indication for curcuma. As the medicinal use of curcuma has been documented continuously in European handbooks, C*urcuma longa* fulfils the requirements of Directive 2004/24 EC for classification of traditional herbal medicinal products. The use of *Curcuma longa* is considered plausible in the treatment of dyspeptic complaints on the basis of bibliography and pharmacological data.
Although the use for skin diseases is also described in authoritative texts, it is not included in the monograph because no data could be found on the preparations and the posology.

The pharmacological activity is attributed to the whole extract; however the majority of activities were also observed with curcumin.

Curcuma longa is used in the following pharmaceutical forms and posology:

- powdered plant material: 1.5-3.0 g daily
- oral infusion: 0.5-1 g up to three times daily
- tincture (1:10): 0.5-1 ml three times daily
- dry extract (13-25:1): 80-160 mg daily, divided in 2-5 partial doses
- dry extract (5.5-6.5:1): 100-200 mg 2 times daily
- tincture (1:5) : 10 ml once daily or 5 ml in 60 ml water 3 times daily

Only mild side effects have been reported for *Curcuma longa*: dry mouth, flatulence, and gastric irritation. No serious side effects have been reported.

Due to lack of data, the use of *Curcuma longa* in children under the age of 18 years cannot be recommended.
As relevant data on the use during pregnancy and lactation is lacking, *Curcuma longa* can not be recommended in these cases.

II ANNEXES

I.5 COMMUNITY HERBAL MONOGRAPH ON CURCUMA LONGA L., RHIZOMA

I.6 LITERATURE REFERENCES