
LEK. SIROV.	God.XXXV	Broj 35	Str. 3 – 21	Beograd 2015.
LEK. SIROV.	Vol.XXXV	No. 35	Pp. 3 – 21	Belgrade 2015.

Pregledni rad – Review paper
UDC: 615.322:665.528.254.82
COBISS.SR-ID 220235788

Manuscript received: 6.12.2015.
Accepted for publication: 11.12.2015.

PHARMACOLOGICAL PROFILE OF TURMERIC OIL: A REVIEW

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SUMMARY

Turmeric (*Curcuma longa*) is a medicinal plant of the family Zingiberaceae widely growing throughout India. Turmeric oil is secondary metabolite of turmeric and obtained by steam distillation of its rhizomes. Turmeric oil a lipophilic fraction from turmeric, exhibits several therapeutic potentials. Turmeric oil chiefly comprises α -turmerone and β -turmerone. During more recent decades broad spectrums of therapeutically interesting pharmacological properties of turmeric and its secondary metabolites have been reported. Recent several efforts made to explore the pharmacological profile and mechanism of action of turmeric revealed exceptionally broad spectrums of pharmacological activity profiles of turmeric oil. It is now well recognized that additive or synergistic interactions between diverse combinations of phytochemicals are involved in health benefits of vegetarian diets and herbal remedies and that regular consumption of appropriate combinations of some such edible phytochemicals with every day meals could as well be used for prevention and cure of different health problems. Critical analysis of available preclinical and clinical information on turmeric oil strongly suggests it is pharmacologically polyvalent and possess several pharmacological properties. Aim of this communication is to summarize and critically analyze such data, and to point out some possibilities for more rationally exploiting their therapeutic potential for discovering novel therapeutic leads, or for obtaining pharmacologically better standardized phyto-pharmaceuticals.

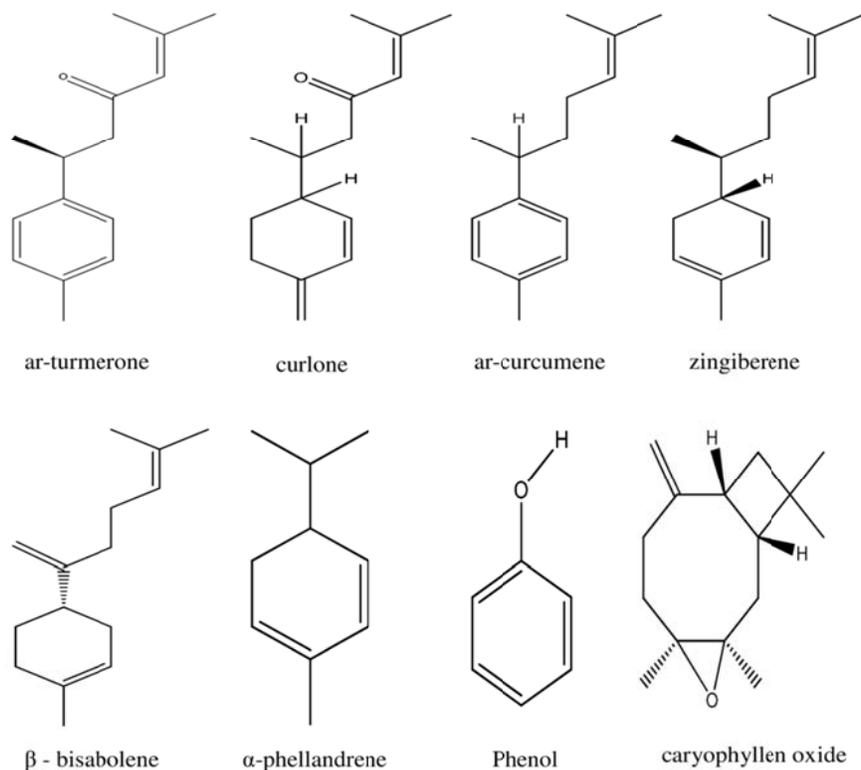
Ključne reči: *Curcuma longa*, Turmeric oil, lipophilic, phyto-pharmaceuticals.

INTRODUCTION

Essential oils are complex mixtures of volatile terpenes selected throughout evolution to protect plants from external threats by various means including mimicking endogenous substrates in herbivores. While biologic and potentially medicinal effects of these essential oils are thus to be anticipated, these compounds are often less well studied than other classes of secondary plant metabolites, with polyphenols being a prominent example. Such is the case for turmeric (*Curcuma longa* L., Zingiberaceae), a medicinal botanical whose rhizome contains two major classes of secondary metabolites, the phenolic curcuminoids and the hydrophobic essential oils. Turmeric (*Curcuma longa* L.) is one of the most widely used ancient herbs, which is traditionally used in several Asian countries for several inflammatory, infectious, fungal and viral ailments. Various preparations derived from turmeric display potential therapeutic effects against cancer, pains, stomach upset, ulcer, dysentery and wounds [1]. Turmeric oil is prepared from the rhizome of turmeric by steam distillation [2]. Turmeric oil is different from oleoresin of turmeric where curcuminoids are the major compounds while α -turmerone is the major constituent of turmeric oil [3]. Several medicinal and pharmacological properties such as antifungal, insect repellent, anti-bacterial, anti-platelet and anti-mutagenic activities of turmeric oil have been reported [4-6]. Turmeric oil also possess anti-inflammatory, antioxidant, anti-arthritic and antinociceptive properties [7]. It has shown efficacy in neuroprotective activity against cerebral ischemia and attenuation of delayed neuronal death via a caspase dependent pathway [8-10]. The chemopreventive efficacy of turmeric oil has been reported against submucous fibrosis in humans [11]. It also acts against benzo [α] pyrene induced DNA damage *in vitro* in oral mucosa cells [12]. Since turmeric oil is highly lipophilic in nature its accessibility to the brain is facilitated and has been found to be protective against stroke [13]. Thus, further evaluations against various biological activities, fractionation and identification of the mechanism of action prior its therapeutic uses are needed.

Turmeric oil also can improve the bioavailability of curcumin after oral administration in humans [14]. Food and Drug Administration (FDA) approved turmeric oil as food additive mentioned as safe drug. There is considerable evidence that the antioxidants contained in fruits, vegetables and beverages play an important role in the maintenance of health, and in prevention of disease. The safety of synthetic antioxidants, such as butylated hydroxyanisole, butylated hydroxytoluene and propyl gallate, is now under scrutiny [15]. Thus, the food industry is undertaking the rapid development and use of natural antioxidants, especially those of plant origin, to replace synthetic food additives. Among these various kinds of natural substances, essential oils from aromatic and medicinal plants receive particular attention as potential natural agents for food preservation.

Figure 1. Major phytochemical constituents from turmeric oil.
Figura 1. Glavne komponente etarskog ulja kurkume.



Moreover, essential oils are proven to have various pharmacological effects, such as spasmolytic, carminative, hepatoprotective, antiviral and anticarcinogenic effects [16]. However, most of the pharmacological activities of turmeric oil have been proved but still efforts are needed to identifying novel therapeutic leads potentially useful for combating comorbid health problems commonly encountered in chronically ill patients. In this communication our current understanding on medicinal phytochemistry of turmeric oil are summarized, and usefulness of its therapeutically interesting pharmacological activity profiles are also pointed out.

PHYTOCHEMICAL CONSTITUENTS

Turmeric oil is isolated by steam distillation from the rhizome of turmeric. The color and appearance of turmeric oil is pale yellow liquid and store at 4 °C away from direct light. GC– MS indicate that the main components of turmeric oil are ar-turmerone (61.79%) and curlone (β - turmerone) (12.48%). Other major and minor ingredients in this essential oil are ar-curcumene (6.11%), phenol (3.45%), zingiberene (2.98%), α -sesquiphellandrene (2.81%), 1-ethyl- 4-isobutylbenzene (2.62%), β -bisabolene (1.48%), benzene (1.48%), benzaldehyde (1.44%), 1,2,3,5-tetramethyl-benzene (1.42%), silane (0.84%), and 4-methyl-carbanilonitrile (1.09%) some other constituents are ar-turmerol, caryophyllen oxide, d-3-carene, α -phellandrene (Fig.1) [2, 4, 17].

THERAPEUTIC INDICATIONS

Antimutagenic activity

Reported biologic properties of the multi-component essential oils of turmeric include antimutagenic and anticarcinogenic activity. Turmeric oil showed significant antimutagenic activity against direct acting mutagens such as sodium azide, 4-nitro-O-phenylenediamine and N-methyl- N-nitro N' nitrosoguanine. Turmeric oil is found to have significant antimutagenic effect against mutagen needing metabolic activation such as 2-acetamidoflourene. Turmeric oil significantly inhibited the mutagenicity induced by tobacco extract to Salmonella strain. DMBA and croton oil induced papilloma development in mice was found to be delayed and prevented significantly by turmeric oil application. Moreover, turmeric oil significantly inhibited isoforms of cytochrome p450 (CYP1A1, CYP1A2, CYP2B1/2, CYP2A, CYP2B and CYP3A) enzymes *in vitro*, which are involved in the activation of carcinogens [18]. Some such therapeutically interesting bioactivities of turmeric oil are summarized in Table 1 and Fig. 2.

Neuroprotective activity

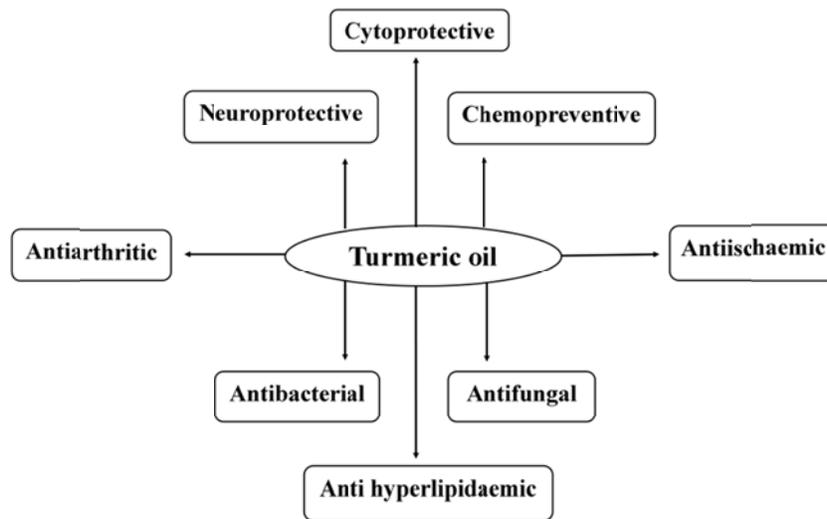
Turmeric oil ameliorates the ischemia induced neurological functional deficits, infarct and edema volumes measured after 24 hrs of ischemia. Immunohistochemical and Western blot analysis demonstrated that the expression of iNOS, cytochrome c and Bax/Bcl-2 were altered after the insult and antagonized by treatment with turmeric oil. Turmeric oil significantly reduces nitrosative stress; it tends to correct the decreased mitochondrial membrane potential and also affects caspase-3 activation [9]. Turmeric oil reduced post-ischemic brain neutrophil infiltration in the ischemic area, controlled tissue nitric oxide levels and the neuronal levels of nitric oxide, peroxyntirite and reactive oxygen species. Double

Table 1. Some reported pharmacological activities of Turmeric oil.**Tabela 1.** Publikovani podaci o farmakološkoj aktivnosti etarskog ulja kurkume.

Pharmacological activities	Dose duration and route of administration	References
Anti-inflammatory activity	100, 500 & 1000 mg/kg, 5 days, i.p.	[2]
Antioxidant activity	100 & 500 mg/kg, 30 days, p.o.	[2]
Antinociception activity	100, 500 & 1000 mg/kg, 1 days, i.p.	[2]
Neuroprotective	250 & 500 mg/kg, 1 day, p.o.	[9,19]
Anti-hyperlipidaemic	30, 100 & 300 mg/kg, 28 days, p.o. 100 & 300 mg/kg, 45 days, p.o	[20,21]
Anti atherosclerosis	100 & 300 mg/kg, 7 days, p.o.	[22]
Antiarthritic activity	56 mg/kg, 10 days, i.p.	[7]
Anti-ischemic	500 mg/kg, 3 days, p.o.	[6]
Antiplatelets	500 mg/kg, 3 days, p.o.	[6]
Liver cirrhosis	100, 200 & 500 mg/kg, 2 weeks, i.p.	[24]
Antifibrosis	100 & 300 mg/kg, 7 days, i.p.	[25]
Disease modifying activity	300 mg/kg, 4 weeks, p.o.	[23]
Cytoprotective	600 mg/kg, 3 months, p.o.	[12]
Anti-apoptogenic	500 mg/Kg, 5 days, i.p.	[10]
Antifungal	459 µg/ml <i>in vitro</i>	[26]
Antibacterial activity	50, 100 & 200 ppm <i>in vitro</i>	[4]
Antidermatophytic	312 µg/mL <i>in vitro</i>	[27]
Antiaflatoxicogenic activity	0.01–5% (v/v) <i>in vitro</i>	[28]
Chemopreventive	50, 100 and 200 µg/ml <i>in vitro</i>	[18]
Superoxide radical scavenging activity	135 µg/ml <i>in vitro</i> 22.6–45.27 µg/ml <i>in vitro</i>	[2,29]
Hydroxyl radical scavenging activity	200 µg/ml <i>in vitro</i> 18.27 µg/ml <i>in vitro</i>	[2,29]
Inhibition of lipid peroxidation	400 µg/ml <i>in vitro</i>	[2]
DPPH radical scavenging activity	1000 µg/ml <i>in vitro</i> 14.45 & 16.58 µg/ml <i>in vitro</i>	[2,29]

immunofluorescence staining analysis and Western immunoblot analysis with turmeric oil treatment showed that the expression of nitric oxide synthase (NOS) isoforms decreased significantly when compared to the untreated ischemia group [19]. It has been also reported that 500 mg/kg turmeric oil dose administration before middle cerebral artery occlusion followed by reflow in rats significantly diminished infarct volume, improved neurological deficit and counteracted oxidative stress. These results suggested that the neuroprotective activity of turmeric oil against cerebral ischemia is associated with its antioxidant activities and further; there is attenuation of delayed neuronal death via a caspase dependent pathway. Such studies confirmed that turmeric oil could be a promising agent not only for the treatment of cerebral stroke, but also for the treatment of other disorders associated with oxidative stress [10].

Figure 2. Some major pharmacological activities of turmeric oil.
Figura 2. Glavne farmakološke aktivnosti etarskog ulja kurkume.



Anti-hyperlipidaemic activity

Moreover, another study revealed that turmeric oil significantly reduced plasma total cholesterol, low-density lipoprotein cholesterol, triglyceride and free fatty acid and increased high-density lipoprotein cholesterol when compared with the high cholesterol group. Similar group comparisons showed that turmeric oil treatment reduced hepatic cholesterol and oxidative stress and improved liver function [20]. It also markedly elevated the activities of superoxide dismutase and

glutathione peroxidase and lowered maleic dialdehyde activity, to suppress oxidative reactions. Besides, histological morphology examination showed that turmeric oil also prevented the damage of liver tissues induced by high fat diet [21].

Anti atherosclerotic activity

Turmeric oil attenuates arterial injury-induced accelerated atherosclerosis, inflammation and macrophage foam-cell formation [22]. The administration of turmeric oil suppressed the mRNA expression of TNF- α , IL-1 β , IL-6 and IFN- γ and increased the expression of TGF- β in peritoneal macrophages. In THP-1 macrophages, turmeric oil supplementation prevented oxidized low density lipoprotein induced production of TNF- α and IL-1 β and increased the levels of TGF- β . The above mentioned study shows that turmeric oil attenuates arterial injury-induced accelerated atherosclerosis, inflammation and macrophage foam-cell formation.

Disease modifying activity

Turmeric oil treatment in hamsters ameliorated hyperlipidaemia, hyperglycaemia, insulin resistance, oxidative stress, inflammation, endothelial dysfunction, platelet activation, and thrombosis. Turmeric oil treatment also in rats ameliorated hyperglycaemia and hyperinsulinaemia by modulating hepatic expression of sterol regulatory element binding protein 1c, peroxisome proliferator activated receptor gamma co-activator-1 α and peroxisome proliferator activated receptor gamma co-activator-1 β genes known to be involved in lipid and glucose metabolism. High fructose feeding to rats and hamsters led to the development of insulin resistance, hyperglycaemia, endothelial dysfunction and oxidative stress. Turmeric oil also prevented development of thrombotic complications associated with insulin resistance perhaps by modulating genes involved in lipid and glucose metabolism [23].

Anti-arthritic activity

Another study of turmeric oil explored its anti-arthritic effect in female rats. It dramatically inhibited joint swelling in female rats with streptococcal cell wall induced arthritis. Oral administration of higher dose turmeric oil was non-toxic, but only mildly joint protective. These results do not support the isolated use of turmeric oil for arthritis treatment, but instead, identify potential safety concerns in vertebrates exposed to turmeric oil [7].

Anti-ischemic activity

Turmeric oil at 500 mg/kg dose was evaluated against myocardial ischemia-reperfusion induced injury in the rat model. Turmeric oil failed to confer protection against cardiac injury, however significant reversal of ADP induced

platelet aggregation was evident in the same animals. Moreover, collagen and thrombin induced platelet aggregation as well as tyrosine phosphorylation of various proteins in activated platelets was also suppressed. Turmeric oil also offered significant protection against collagen-epinephrine induced thrombo embolism in mice as well as augmented total time to occlusion against FeCl₃ induced arterial thrombosis in rats [6].

Hepatoprotective activity

Turmeric oil was found to reverse those changes of serum levels observed in the cirrhotic rats and the 200 mg/kg treated group showed the most obvious reverse tendency with significantly decreased alanine amino transferase, aspartate aminotransferase and increased albumin levels. The results indicated that turmeric oil with the dose of 100 mg/kg could inhibit the activities of CYP450 isoforms CYP2C9 and CYP2D6 *in vivo* in cirrhotic rats, while dose of 400 mg/kg could induce the activity of CYP2C19 [24].

Antifibrosis activity

Turmeric oil also demonstrating protective and anti-fibrosis activities in renal fibrosis. Nuclear magnetic resonance based metabonomics combined with clinical chemistry and histopathology examination were performed to evaluate intervening effects of Turmeric oil on renal interstitial fibrosis rats induced by unilateral ureteral obstruction. The metabolite levels were compared based on integral values of serum ¹H NMR spectra from rats on 3, 7, 14, and 28 days after the medicine administration. Time trajectory analysis demonstrated that metabolic profiles of the agent treated rats were restored to control levels after 7 days of dosage. The results confirmed that the agent would be an effective anti-fibrosis medicine in a time-dependent manner, especially in early renal fibrosis stage. The results of some other study substantiated that turmeric oil administration can ameliorate renal fibrosis symptoms by inhibiting some metabolic pathways, including lipids metabolism, glycolysis and methylamine metabolism [25].

Antidermatophytic activity

Turmeric oil was studied against fifteen isolates of dermatophytes, four isolates of pathogenic molds and six isolates of yeasts. The inhibitory activity of turmeric oil was tested in Trichophyton-induced dermatophytosis in guinea pigs. The results showed that all 15 isolates of dermatophytes could be inhibited by turmeric oil at dilutions of 1:40-1:320. The other four isolates of pathogenic fungi were inhibited by turmeric oil at dilutions of 1:40-1:80. In the experimental animals, turmeric oil (dilution 1:80) was applied by dermal application on the 7th day following dermatophytosis induction with Trichophyton rubrum. An

improvement in lesions was observed in 2-5 days and the lesions disappeared 6-7 days after the application of turmeric oil [26].

Antibacterial activity

The mother liquor after isolation of curcumin from oleoresin contains approximately 40% oil. The oil was extracted from the mother liquor using hexane and the hexane extract was separated into three fractions using silica gel column chromatography. These fractions were tested for antibacterial activity by pour plate method against *Bacillus cereus*, *Bacillus coagulans*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Fraction eluted with 5% ethyl acetate in hexane was found to be most active fraction for the antibacterial activity [4].

Antifungal activity

Some previous studies on turmeric oil reported effective antifungal activity against dermatophytes, a group of fungi that causes skin diseases. In mentioned study turmeric creams containing 6 and 10% w/w turmeric oil were prepared and tested against clinical strains of dermatophytes using broth dilution technique. Minimum fungicidal concentrations of turmeric creams were found to be 312 $\mu\text{g/mL}$. Ar-turmerone, a major compound separated from turmeric oil, promoted more effective antidermatophytic activity with the MICs of 1.56–6.25 $\mu\text{g/mL}$, compared to 3.90–7.81 $\mu\text{g/mL}$ of standard ketoconazole. The results indicated that turmeric oil in the cream was suitable to be formulated as antidermatophytic preparation [27]. Some other pharmacological properties of ar-turmerone are summarized in Table 2.

Table 2. Some reported pharmacological activities of ar-turmerone.

Tabela 2. Publikovani podaci o farmakološkoj aktivnosti ar-turmerona.

Pharmacological activities	Dose, duration and route of administration	References
Antidepressant	2.5 and 5.0 mg/kg, 7 days, p.o.	[34]
Antiepileptic	50 mg/kg, single dose, i.p.	[39]
Antidermatophytic	1.56-6.25 $\mu\text{g/ml}$ <i>in vitro</i>	[27]
Antitumor activity	200 and 300 mg/kg, 10 days, p.o. 20-50 $\mu\text{g/ml}$ <i>in vitro</i>	[30,40]
Antidiabetic	20-100 mg/kg, 4 weeks, p.o.	[32]
Antiplatelet activity	10 and 100 $\mu\text{g/ml}$ <i>in vitro</i>	[33]

Antiaflatoxicogenic activity

Aflatoxins are highly toxic, mutagenic, teratogenic and carcinogenic mycotoxins. Consumption of aflatoxin contaminated food and commodities possess serious hazards to the health of humans and animals. Turmeric oil also contains the antiaflatoxicogenic activities. According to mentioned report medium tests were prepared with the turmeric oil at concentrations varied from 0.01% to 5.0%. All doses of the essential oil of the plant interfered with mycotoxin production. Turmeric oil significantly inhibited the production of aflatoxins; the 0.5% level had a greater than 96% inhibitory effect. The levels of aflatoxin B1 production were found to be 1.0 µg/mL, for the samples treated with the turmeric oil at a concentration of 0.5% [28].

Antioxidant activity

The antioxidant activity of the oil was evaluated by using 2, 2- diphenyl-1-picrylhydrazyl (DPPH) and superoxide radical-scavenging assays. The oil showed potent DPPH radical-scavenging activity ($IC_{50} = 14.45 \mu\text{g/ml}$), which was higher than butylated hydroxyanisole ($IC_{50} = 18.27 \mu\text{g/ml}$). The results indicate that the turmeric oil could serve as an important bio-resource of antioxidants for using in the food industries [29]. In an another study turmeric oil was found to have *in vitro* antioxidant activity and IC_{50} for scavenging superoxides, hydroxyl radicals, and lipid peroxidation were 135 µg/ml, 200 µg/ml, and 400 µg/ml, respectively. The ferric-reducing activity for 50 µg of turmeric essential oil was found to be 5 mM. Intraperitoneal administration of oil was found to inhibit PMA-induced superoxide radicals elicited by macrophages. However, oral administration of turmeric oil for one month to mice significantly increased superoxide dismutase, glutathione, and glutathione reductase enzyme levels in blood and glutathione-S-transferase and superoxide dismutase enzymes in liver [2]. Therefore, results demonstrated that turmeric oil could be use for potential health benefits as it is potent antioxidant in nature.

Antiapoptotic activity

Major constituent of turmeric oil ar-turmerone found to be antiapoptotic in nature. It inhibited the increase in the number of white blood cells, which normally increase by the injection of lymphoblast cells, or P388D1, and increased lymphocyte percentage compared to the control. Tumor inhibition rate in the ar-turmerone treated group was 11.79%, and the apoptosis indexes of the control and ar-turmerone were 4.22 ± 1.02 and 5.45 ± 1.46 respectively [30]. It shown that ar-turmerone has a repressive effect on P388D1 lymphocytic leukemia. It is also suggested that this protective effect of ar-turmerone from P388D1 lymphocytic leukemia resulted from the increased activity of tumor immunogenicity through increased T-lymphokine production and increased percentage of lymphocytes. Another report based on

pharmacological profile of ar-turmerone, the major compound present in turmeric oil also shown to exhibit its anticancer properties [31].

Anti hyperglycemic activity

It has been reported in elsewhere, that turmeric extracts were obtained by ethanol extraction (E-ext) to yield curcuminoids and sesquiterpenoids, hexane extraction (H-ext) to yield sesquiterpenoids, and ethanol extraction from hexane-extraction residue (HE-ext) to yield curcuminoids. The control group was fed a basal diet, while the other groups were fed a diet containing 0.1 or 0.5 g of H-ext or HE-ext/100 g of diet or 0.2 or 1.0 g of E-ext/100 g of diet for 4 weeks. Although blood glucose levels in the control group significantly increased after 4 weeks, feeding of 0.2 or 1.0 g of E-ext, 0.5 g of H-ext, and 0.5 g of HE-ext/100 g of diet suppressed the significant increase in blood glucose levels. Furthermore, E-ext stimulated human adipocyte differentiation and these turmeric extracts had human peroxisome proliferator-activated receptor- γ (PPAR- γ) ligand-binding activity in a GAL4-PPAR- γ chimera assay. Also, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone had PPAR- γ ligand-binding activity. These results indicate that both curcuminoids and sesquiterpenoids in turmeric exhibit hypoglycemic effects via PPAR- γ activation as one of the mechanisms, and suggest that E-ext including curcuminoids and sesquiterpenoids has the additive or synergistic effects of both components [32].

Antiplatelet activity

The active constituent from turmeric oil was isolated and characterized as ar-turmerone by various spectral analyses. At 50% inhibitory concentration (IC_{50}) value, ar-turmerone was effective in inhibiting platelet aggregation induced by collagen (IC_{50} 14.4 μ M) and arachidonic acid (IC_{50} 43.6 μ M). However, ar-turmerone had no effect on platelet activating factor or thrombin induced platelet aggregation. In comparison, ar-turmerone was significantly more potent platelet inhibitor than aspirin against platelet aggregation induced by collagen. These results suggested that ar-turmerone could be useful as a lead compound for inhibiting platelet aggregation induced by collagen and arachidonic acid [33].

Antidepressant and Immunostimulant activity

Ar-turmerone has been also reported as antidepressant agent as at oral dose of 2.5, and 5.0 mg/kg, significantly reduced the immobility time of mice in both the forced swim test and tail suspension test, but it did not significantly affect the ambulatory and total movements of mice. In addition, ar-turmerone decreased the corticosterone level in the blood while it increased the levels of 5-HT in cortex, striatum, hippocampus, and hypothalamus, the level of NE in striatum and hippocampus, the levels of 3-methoxy-4-hydroxyphenylethylglycol (MHPG) and

dihydroxyphenylacetic acid (DOPAC) in hypothalamus, the level of 5-hydroxyindoleacetic acid in striatum, and the level of DA in striatum, hippocampus, and hypothalamus. Ar-turmerone also decreased the activity of MAO-A in the frontal cortex and hippocampus of mouse brain [34]. Aromatic turmerone (Ar-turmerone) was shown to have immunostimulating activities in human peripheral blood mononuclear cells by stimulation of peripheral blood mononuclear cells proliferation and cytokine production. It also activated caspase cascade by a significant decrease of procaspases-3, 8 and 9 [35].

CLINICAL STUDIES

Oral submucous fibrosis, a chronic disease characterized by fibrosis of oral mucosa, is a premalignant condition carrying a high risk of malignant transformation. *In vitro* studies on the effect of turmeric oil and turmeric oleoresin on the incidence of micronuclei in lymphocytes from normal healthy subjects showed that the test compounds did not cause any increase in the number of micronuclei as compared with those found in untreated controls. Further it was observed that all three compounds offered protection against benzo[*a*]pyrene induced increase in micronuclei in circulating lymphocytes. In subsequent studies, patients suffering from oral submucous fibrosis were given a total oral dose of turmeric oil (600 mg TO mixed with 3 g TE/day), turmeric oleoresin (600 mg + 3 g TE/day) and 3 g turmeric extract/day as a control for 3 months. It was observed that all three treatment modalities decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes. Turmeric oleoresin was found to be more effective in reducing the number of micronuclei in oral mucosal cells but in circulating lymphocytes the decrease in micronuclei was comparable in all three groups [12]. This is another clinical study which was carried out to evaluate the efficacy of curcumin capsule and turmeric oil in patient with oral submucous fibrosis both clinically and histopathologically to compare them with conventional chemopreventive treatment. After treatment and follow up statistically significant improvement was observed in clinical sign and symptoms of patient treated with curcumin capsule and turmeric oil when compared to those with multinal. Positive changes were also observed in the histopathological examination after treatment with curcumin capsule and turmeric oil [11].

BIOAVAILABILITY

It has been reported that turmeric oil enhances the bioavailability of curcumin in human (BCM-95) as well as clinical study is ongoing to assess the efficacy and safety of BCM-95 in oral premalignant lesions as well as cervical cancers [14]. The major ingredient of turmeric oil determined by GC/MS is

reported to be ar-turmerone and its bioavailability was reported to be 13% [2, 5]. Such results indicate that turmeric oil has a significant medicinal value which has not been exploited yet. The effects of turmerones on curcumin transport were evaluated in human intestinal epithelial Caco-2 cells. The roles of turmerones on P-glycoprotein (P-gp) activities and mRNA expression were also evaluated. Results showed that in the presence of α -turmerone and ar-turmerone, the amount of curcumin transported into the Caco-2 cells was significantly increased. α -turmerone and verapamil (P-gp inhibitor) significantly inhibited the efflux of rhodamine-123 and digoxin via inhibited the activity of P-gp. It is interesting that aromatic turmerone significantly increased the rhodamine-123 efflux and Pgp (MDR1 gene) mRNA expression levels. The presence of turmerones did affect the absorption of curcumin *in vitro*. These findings suggest the potential use of turmeric extract (including curcumin and turmerones), rather than curcumin alone, for treating diseases. In conclusion, the transport of curcumin in Caco-2 cell monolayers could be enhanced in the presence of turmerones, which were isolated from turmeric crude extract. The two turmerones showed opposite effects on P-gp activities: aromatic turmerone inhibited the P-gp activities, whereas α -turmerone enhanced P-gp activities as well as up-regulated MDR1, MRP2 and BCRP expressions in Caco-2 cells. These findings supported the use of turmeric extract (including curcumin and turmerones), other than curcumin alone in cancer patients, especially those with colorectal cancers [36]. In view of the long term administration required for cancer prevention a Phase I clinical trial of turmeric oil was conducted to study the safety and tolerance of turmeric oil in volunteers for a period of 3 months. Nine healthy volunteers were tested for haemoglobin, blood counts, liver and kidney functions, bleeding and clotting time and serum electrolytes initially and at 1 and 3 months of treatment. They were administered 0.6 ml of turmeric oil three times a day for 1 month and 1 ml in 3 divided doses for 2 months. The acute tolerability study on Day 1 was conducted in a Clinical Pharmacology day care Unit. Volunteers were daily supervised for turmeric oil intake as well as for any side effects throughout the study period. There was no clinical, haematological, renal or hepatic-toxicity of turmeric oil. In view of the potential for reversing oral submucous fibrosis, a precancerous condition for oral cancer, turmeric oil has been recommended directly for a Phase II trial in patients [37].

TOXICITY

Some studies reported that turmeric oil is safe even at high dose. Food and Drug Administration (FDA) approved turmeric oil usage as food additive and is listed as Generally Recognized As Safe (GRAS), while the FDA's GRAS list does not include the dosage of turmeric oil. Turmeric oil is usually used in aroma therapy and the recommended dose is 1–2 drops/day. Acute administration of

turmeric oil was done as single dose up to 5 g of turmeric oil per kg body weight and subchronic toxicity study for thirteen weeks was done by daily oral administration of turmeric oil at doses 0.1, 0.25 and 0.5 g/kg body weight in wistar rats. There were not found any mortality, adverse clinical signs or changes in body weight, water and food consumption during acute as well as subchronic toxicity studies. Indicators of hepatic function such as aspartate aminotransferase, alanine amino transferase and alkaline phosphatase were unchanged in treated animals compared to untreated animals. Oral administration of turmeric oil for 13 weeks did not alter total cholesterol, triglycerides, and markers of renal function, serum electrolyte parameters and histopathology of tissues. Turmeric oil did not produce any mutagenicity to *Salmonella typhimurium* TA-98, TA-100, TA-102 and TA-1535 with or without metabolic activation. Administration of turmeric oil to rats (1 g/kg b.wt.) for 14 days did not produce any chromosome aberration or micronuclei in rat bone marrow cells and did not produce any DNA damage as seen by comet assay confirming the non toxicity of turmeric oil. Anti-arthritis evaluation of turmeric oil in mice was carried out at doses of 560 mg/kg body weight [7]. Turmeric oil (0.1–3 mg/plate) did not produce any revertants during Ames test, indicating that there was no significant dose related mutagenicity of the turmeric oil either with or without metabolic activation. Genotoxic substances are potentially known to be mutagenic or carcinogenic. Exposure of cells to genotoxic substances damage chromosomes of the mitotic spindle leading to the formation of micronuclei. Genotoxic studies of turmeric oil such as micronuclei formation, chromosomal aberrations and genomic DNA damage analysis by comet assay have revealed that there was no genotoxic effect after 2 weeks oral administration of 1 g/kg body weight turmeric oil [38].

CONCLUSION

As like many other medicinal plants turmeric also produces structurally and functionally diverse bioactive secondary plant metabolites, not all of which can be extracted by a single solvent or extraction procedure. Moreover, therapeutically interesting bioactivity profile of a given plant extract is not only a resultant of the combined effects of all bioactive ingredients present in it, but also depends on its treatment regimen used to define its activity profile. Complexities arising from these facts clearly indicate that translation of traditional knowledge on medicinal uses of turmeric or of any other medicinal plant, in terms of modern medical sciences is possible only when the plant is considered as a whole, and its diverse types of extracts are tested in a battery of therapy relevant animal models. Hereupon, we have paid attention to the pharmacological activity profiles of the turmeric oil. Turmeric oil contains several interesting pharmacological activities. Due to lipophilic in nature it also facilitates the transportation of curcuminoids

across the membrane and increases its bioavailability. Several reports confirm the fact that turmeric oil is safe even at a high dose. Even then turmeric oil is not explored as a potent therapeutic agent. It is now well established that all chronic diseases or illnesses, always cause mental health problems, and that bi-directional interactions between mental health problems and physical health is a common feature of almost all socioeconomically important health problems. Unfortunately, even today, modern medicinal phytochemists and pharmacologists pay little attention to these facts and continue to explore traditionally known medicinal plants as sources for structurally and functionally novel therapeutic lead molecules only. Lessons learned and experiences gained from extensive efforts made since decades strongly suggest that turmeric oil could be a valuable and potential therapeutic agent.

ACKNOWLEDGEMENT

Suruchi Verma graciously acknowledged the Department of Science and Technology, New Delhi, Government of India, for awarding INSPIRE Fellowship (IF131112).

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FARMAKOLOŠKI PROFIL ETARSKOG ULJA KURKUME

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IZVOD

Kurkuma (*Curcuma longa*), lekovita biljka iz porodice Zingiberaceae, široko je rasprostranjena širom Indije. Njeno etarsko ulje, produkt sekundarnog metabolizma, dobija se destilacijom vodenom parom iz rizoma. Ulje je po prirodi lipofilno i ispoljava veliki terapijski potencijal. Ulje kurkume se uglavnom sastoji od α -turmerona i β -turmerona. Tokom poslednjih par decenija publikovani su brojni radovi na temu terapijski zanimljivih farmakoloških osobina kurkume i njenih sekundarnih metabolita. Skorašnji naponi da se istraži farmakološki profil i mehanizam delovanja kurkume otkrili su izuzetno širok spektar farmakološke aktivnosti kurkuma ulja. Sada je već dobro poznato da se aditivne ili sinergijske interakcije među različitim kombinacijama fitohemijskih jedinjenja smatraju benefitima vegetarijanske ishrane i biljnih lekova za ljudsko zdravlje, i preporučuju se odgovarajuće kombinacije takvih jestivih fitohemikalija u svakodnevnoj ishrani kao i njihovo korišćenje u prevenciji i lečenju različitih zdravstvenih problema. Kritička analiza raspoloživih prekliničkih i kliničkih informacija o ulju kurkume snažno sugerise kako je ono farmakološki polivalentno i poseduje razna farmakoloških svojstava. Cilj ovog rada je da sumira i kritički analizira prikupljene podatke o ulju kurkume i ukaže na mogućnosti racionalnijeg iskorišćavanja njegovog terapijskog potencijala radi otkrivanja novih terapijskih mogućnosti ili dobijanja farmakološki standardizovanih fito-preparata.

Ključne reči: *Curcuma longa*, etarsko ulje kurkume, lipofilno, fitofarmaceutika.