

# TURMERIC

## *Curcuma longa* L.

### *Family*

Zingiberaceae.

*Curcuma domestica* Valetton is one of 10 synonyms.<sup>1,2</sup>

### *Parts Used*

Dried rhizome.

### *Description*

Turmeric (pronounced tur-mer-ic or too-mer-ic depending on where you live) is a stemless, leafy perennial herb closely resembling ginger (*Zingiber officinale*) and grows up to 1.5 metres tall. The large, broad, hairless, light green leaves arise from near ground level and are borne at the top of the non-woody underground stem, with overlapping petioles. They are 30 to 40cm long and eight to 12cm wide,

and are thin, oval-shaped and elongated. Attractive pale yellow and white bell-shaped flowers emerge in short oblong spikes developing in the centre of the leaves. The fleshy, smooth, branched rhizomes are bright orange outside and bright orange to yellow within. Turmeric is a sterile plant and does not produce any seeds. It is extensively cultivated in India, China, Indonesia, islands of the Caribbean, South America and other tropical countries.<sup>3,4</sup>

### *Traditional Use*

Although in medicinal use in Asia for more than 2500 years, turmeric is probably better known in the West as a common yellow spice. It is used as one of the principle, pungent flavouring ingredients in curries and widely used in the food industry as a colouring agent (as a food additive, curcumin's code number on food labels is 100).<sup>5</sup>



Unlike its close botanical relative, ginger, it never caught on in the West as a medicinal herb. Until recently Western medicine viewed turmeric primarily as a spice with minor aromatic digestive stimulant and hepatic stimulant properties indicated, but little used, for functional hepatobiliary disorders. In the 1930s it was mentioned in the classic book *A Modern Herbal*, the first comprehensive encyclopaedia of herbs to appear since the days of Culpeper (1600s). The author Maude Grieve's only medicinal reference to turmeric is 'it was once a cure for jaundice'.<sup>6</sup> In 1985 the German Commission E approved turmeric root for dyspeptic conditions, although the herb was absent from both the 1983 and 1996 edition of the British Herbal Pharmacopoeia. The long established image of turmeric as a commercial dyestuff, and a component of curry, have been partly responsible for overshadowing its importance as a medicinal herb in the West.<sup>7,8</sup>

However, in this 2017 monograph update, this venerated spice is now reaching iconic status with the West discovering it through the hipster trend of golden milk (haldi-doodh) or turmeric latte, a combination of nut milk and turmeric root, which is 2017's drink of choice and is a healthy alternative to coffee (see recipe below). Turmeric lattes are now being sold in cafes from Sydney to San Francisco, and the drink is gaining fans in the UK. Google searches for turmeric have surged by 300% over the last five years according to data provided by the search engine in its 2016 Food Trends Report. Along with coconut oil, ghee and homemade yoghurt becoming commercial products in the West it would appear that South Asia is well ahead of hipster subculture.<sup>9</sup>

The name turmeric originated from the Medieval Latin name *terramerita*, which became *terre merite* in French, meaning 'deserved earth' or 'meritorious earth', a name by which powdered turmeric was known in commerce. *Curcuma* derives from the Persian word *kurkum* meaning 'saffron' because the orange-yellow rhizome hue is reminiscent of saffron. Marco Polo, in 1280 A.D., mentioned turmeric as growing in the Fokien region of China and is reported to have said "I have found a plant that has all the qualities of saffron, but it is a root." The epithet *longa* refers to the long, tubular roots.<sup>10</sup>

Turmeric is known as Haridra (the yellow one) in Sanskrit and holds a place of honour in India's traditional Ayurvedic system of medicine. It has been a mainstay in curries on the Indian subcontinent for thousands of years and gives curry blends their yellow colour. In addition to its role in cooking, the herb was used for the preservation of food and valued more than gold or precious stones. It was later used commercially as a colouring agent for various items including cotton, silk, paper, wood, foods and cosmetics. Touted by researchers as 'Indian solid gold', 'a spice for life' and 'an age old herb for old age', it is considered a symbol of prosperity and known as a cleanser for the whole body. Turmeric has been used through the ages as a 'herbal aspirin' and 'herbal cortisone' to relieve discomfort and inflammation associated with an extraordinary spectrum of infectious and autoimmune diseases. As a sacred and auspicious item, turmeric has become associated with many Hindu customs and traditions and has been used extensively in various Indian ceremonies for millennia. It is used in every part of India during weddings and other religious ceremonies.<sup>11,12,13,14</sup>

It was highly esteemed by the ancient Indo-European people for its golden-yellow dye resembling sunlight. This culture, known as Arya, worshipped the solar system and attributed special protective properties to those plants, which, like turmeric, contained sun-coloured yellow dyes. In India it can be identified by scores of synonyms, many of which make reference to night. This may be derived from a tradition which required that married women apply turmeric on their cheeks in the evening, in anticipation of a visit by the goddess, Lakshmi, at that time. This custom, still practiced mostly in South India, is probably a remnant of an ancient sun-worship tradition.<sup>15</sup>

Turmeric exemplifies a herb for which clinical applications have evolved over time. Since the time of Ayurveda (1900 BC) numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, especially anti-inflammatory, including such ailments as gynaecological problems, gastric problems, hepatic disorders, infectious diseases and blood disorders. Modern science has provided the scientific basis for the use of turmeric against such disorders.

Boiled with milk and sugar, it has been a traditional remedy for colds. The inhalation of the fumes of burning turmeric causes copious mucous discharge and is said to give instant relief in chronic catarrh. Externally it has been used in the prevention and treatment of skin diseases. The juice of the fresh rhizome is used in parasitic skin infections and turmeric powder rubbed down with oil has been applied to soften rough skin. In chickenpox a coat of turmeric is applied to facilitate the process of scabbing.<sup>16,17</sup>

Traditional Chinese physicians see turmeric (known as jiang huang which translates as 'ginger-yellow') as a warm, pungent, bitter herb related to the spleen, stomach and liver. Its actions are to regulate and move blood, move, regulate and descend Qi, dispel damp-wind, break up blood stasis and relieve pain. In Chinese medicine it is used for menstrual problems such as amenorrhoea and dysmenorrhoea, pain in the chest, abdomen, muscle and joint complaints, and to support liver function and treat jaundice.<sup>18</sup>

In these two systems of medicine (Ayurveda and Chinese), turmeric has been shown to improve gynaecological conditions such as regulating the female reproductive system, purifying the uterus and breast milk. It has also been shown to help relieve the pain of labour. In the last two weeks of pregnancy the mother should take two to three grams a day in warm organic milk. This old remedy is said to simplify the birth, increase the health of mother and child, and decrease the pain of the birth.<sup>19</sup> However, scientific evidence proving these benefits is lacking.<sup>20</sup>

Curcumin, which gives the yellow colour to turmeric, was first isolated by Vogel in 1842, and its chemical structure as diferuloylmethane was determined by Lampe and Milobedeska in 1910.

In the 1870s chemists noticed that turmeric's orange-yellow root powder turned reddish brown when exposed to alkaline chemicals. This discovery led to the development of 'turmeric paper', thin strips of tissue brushed with a decoction of turmeric, then dried. During the late 19th century, turmeric paper was used in laboratories around the world to test for alkalinity. Eventually it was replaced by litmus paper which is still used today.<sup>21</sup>

Pharmacological investigations into the anticancer and anti-inflammatory properties of turmeric and its constituents began to attract research interest in the 1980s. Currently, curcumin is regarded as a natural compound of great interest and of considerable therapeutic potential because of its multiple properties which include antioxidant, anti-inflammatory, chemopreventative, antimutagenic, anticarcinogenic, antimetastatic, antiangiogenic and cardioprotective activities. Although initially it was believed that the activities of turmeric were mainly due to curcumin, research conducted during the 2000s and beyond has identified numerous chemical entities from turmeric and modern science has provided a logical basis for the safety and efficacy of turmeric against human disease.<sup>22,23</sup>

Although this research currently constitutes a rapidly expanding body of literature, a 2003 therapeutic monograph on turmeric by the European Scientific Cooperative on Phytotherapy (ESCOP) echoes the original 1985 Commission E indications for 'symptomatic treatment of mild digestive disturbances and minor biliary dysfunction.'<sup>24</sup>

### Constituents

To date, around 235 compounds, primarily phenolic compounds and terpenoids, have been identified in turmeric. The following are the most well-known. Curcuminoids: Yellow to orange pigments (3 to 5%), mainly diarylheptanoids, with curcumin (diferuloylmethane or curcumin I), demethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III) as the main constituents; volatile oil (3 to 5%) is rich in bisabolane, guaiane and several germacrane-type sesquiterpenes including alpha and beta turmerone, curlone, cucumol and zingiberene; polysaccharide (arabino-galactan ukonan A); calebin A, vanillic acid and vanillin are other phenylpropene and phenolic compounds identified from turmeric. The contents of curcuminoids in turmeric rhizomes vary often with varieties, locations, sources and cultivation conditions, and significant variations have been observed in composition of essential oils of turmeric rhizomes with varieties and geographical locations. Furthermore, both curcuminoids and essential oils vary in content with different extraction methods and under some conditions are

unstable with extraction and storage processes. For example curcumin I is absorbed poorly by the gastrointestinal tract and/or undergoes presystemic transformation. As a natural colouring agent, it is known to be unstable particularly under alkaline conditions, light and high temperature. All curcuminoids are stable when they are kept under minimum light conditions. It has been found that the stability of curcumin I in aqueous solution is strongly increased by the presence of some antioxidants. But the presence of other curcuminoids (II and III), which are antioxidants, seem not to prevent degradation of curcumin I. Isolation of pure curcumin I from turmeric is difficult and time-consuming, and thus the commercial "pure" curcumin I is in fact a mixture of at least three curcuminoids. Such curcuminoids can decompose rapidly but curcuminoids in both turmeric powder and extracts are more stable. Ethanol extraction has shown advantages in both effective extraction and stability of active curcuminoids. Among different extraction solvents, ethanol extraction gives the highest yield of curcuminoids. As a result, commercial turmeric products (whole rhizomes, ground turmeric, turmeric oils, turmeric oleoresin and 'curcumin') have significant variations in composition of bioactive compounds.<sup>25,26,27,28</sup>

### *Actions*

Anti-inflammatory, antioxidant, neuroprotective, anticarcinogenic, antiproliferative, chemopreventive (to reverse, suppress or prevent the development of cancer), antimutagenic, immunomodulator, radioprotective, hepatoprotective, antiulcer, hypolipidaemic, antiatherogenic, analgesic, antimicrobial, antiviral, antifungal, nephroprotective, antidepressant, antiaging, larvicidal, insecticidal.

### *Pharmacological Activity*

Although much has been published about curcumin, comparatively little is known about turmeric itself. When this monograph was first published four years ago, in 2013, a search of curcumin on Pubmed<sup>29</sup> (a public domain, bibliographic reference source) returns more than 5800 articles (in this 2017 update that has almost doubled to 10528), while turmeric returned less than half that, with just over 2500 articles (in 2017 it is 4098), which on closer

inspection are mostly on curcumin. Therefore, data from studies investigating use of turmeric extracts, or other preparations of the whole spice, are limited, especially those comparing the potential of turmeric with curcumin.<sup>30</sup>

Nevertheless, epidemiologic data indicates that some extremely common cancers in the Western world are much less prevalent in regions (e.g. Southeast Asia) where turmeric is widely consumed in the diet.<sup>31</sup> Cell-based studies have demonstrated the potential of whole turmeric as an antimicrobial, insecticidal, larvicidal, antimutagenic, radioprotector and anticancer agent. Numerous animal studies have shown the potential of this spice against proinflammatory diseases, cancer, neurodegenerative diseases, depression, diabetes, obesity and atherosclerosis. At the molecular level, like curcumin, it has been shown to modulate numerous cell signalling pathways and in more than a dozen human clinical trials turmeric has shown safety and efficacy against numerous human ailments including lupus nephritis, cancer, diabetes, irritable bowel syndrome, acne and fibrosis.<sup>32</sup> There are numerous ongoing trials evaluating the efficacy of turmeric in humans and there are a number of completed studies, however the results are yet to be published. For example an Iranian study was conducted to see whether (500mg tid orally for eight weeks) turmeric can be effective in the treatment of pruritus in haemodialysis patients with end stage renal failure. (In this 2017 monograph update the study is completed and the results are published. This was a double-blind placebo-controlled trial conducted on 100 haemodialysis patients suffering from pruritus. Patients were randomised into two groups: turmeric and placebo. The pruritus score and biochemical determinants including high-sensitivity C-reactive protein (hs-CRP) were compared before and at the end of the study between the two groups. The mean decrease in hs-CRP was significantly higher in the turmeric than the placebo group. Also reduction of pruritus scores was greater in the turmeric than the placebo group. The results of this study demonstrate the possible efficacy of turmeric in decreasing hs-CRP and uremic pruritus in end stage renal disease patients.)<sup>33</sup> Another study investigated whether turmeric (500 mg tid for 45 days) is effective in improving diabetic nephropathy and in decreasing the amount of proteinuria and

cytokine levels. These study results have not yet been posted. A phase II clinical trial from France aimed to determine the efficacy and tolerance on 15 days of a turmeric extract (Arantal) in patients with osteoarthritis of the knee (gonarthrosis). These study results have not yet been posted either.<sup>34</sup>

Although turmeric has shown therapeutic efficacy against many human ailments, one of the key problems with turmeric is the poor bioavailability of its constituents. Major reasons contributing to the low plasma and tissue levels of the key constituent of turmeric, curcumin, appear to be due to poor absorption, rapid metabolism and rapid systemic elimination. Many of the animal studies involve parenteral (bypassing the mouth, usually injection) administration and oral curcumin, or turmeric, is likely to be far less active because curcumin is poorly absorbed by the gastrointestinal tract and only trace amounts appear in the blood after oral intake. To improve the bioavailability of curcumin, numerous approaches have been undertaken like the use of piperine that interferes with glucuronidation, the use of liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complex and structural analogues of curcumin. Curcumin may, however, have a local action on the gastrointestinal tract and systemic effects may occur at very low concentrations of curcumin.<sup>35</sup>

Because of the extremely low bioavailability of curcumin the interpretation of some studies is particularly controversial and the clinical relevance of the numerous pharmacological studies on curcumin (or its intravenous use) is uncertain and remains to be established. The majority of recent scientific studies on turmeric employ purified laboratory-grade diferuloylmethane or curcumin I, which should be noted before extrapolating to mixtures of curcuminoids or to crude whole herb extracts. The biotransformation products of curcumin need to be further studied, since oral doses of curcumin have exerted significant activity in several experimental models and clinical trials.<sup>36,37</sup>

Further to this, a ground breaking 2017 review of previous curcumin studies, published in the *Journal of Medicinal Chemistry*, is not complimentary of the curative properties of curcumin suggesting it should no longer be known as 'curecumin'. Both the scientific literature and the molecule's

established properties show that it isn't the silver bullet its proponents claim it to be. There are more than 15,000 manuscripts published related to the biological interactions of curcumin, with 50 more manuscripts published each week, however in this 2017 monograph update according to the review no double-blinded, placebo controlled clinical trial of curcumin has been successful. The damning review of the essential medicinal chemistry of curcumin, in relation to developing a therapeutic drug, provides evidence that curcumin is an 'unstable, reactive, nonbioavailable compound'. The review authors say curcumin is a 'highly improbable lead' for scientists to pursue. They also compare it to a missile that has 'shown excellent promise' to hone in on disease-causing factors, but is beset by failure to make it off the launch pad without exploding. There have been dozens of studies on curcumin yet not a single approved drug based on it. The review attempts to determine why something could work in a petri dish study and not in people. It has to do with 'false positives' meaning curcumin has properties in common with other molecules that make it difficult to study. Curcumin molecules are often mistaken for compounds that have been scientifically proven to be useful in the treatment of various diseases. The researchers present evidence that curcumin is most probably an invalid lead compound as can be shown by a critical evaluation of its PAINS (pan assay interference compounds) and IMPS (invalid metabolic panaceas) characteristics. PAINS are chemical compounds that are often false positives in high-throughput screens (a method for scientific experimentation especially used in drug discovery). PAINS tend to non-specifically react with numerous biological targets rather than specifically affecting one desired target. IMPS are mostly natural compounds which seem to have all sorts of biological activity but nothing that amounts to a useful clinical effect. Curcumin is among the worst offenders routinely giving off false results and throwing studies into doubt. Many of the '5,600 peer reviewed' studies that found benefits were likely rendered useless by the molecule's tendency to look like other molecules. The paper says "many researchers have described the potential 'dark side of curcumin': the drawbacks noted for curcumin include its poor pharmacokinetic/ pharmacodynamics properties, low efficacy in

several disease models, and toxic effects under certain testing conditions. These cautionary reports appear to have been swept away in the torrent of papers, reviews, patents, and Web sites touting the use of curcumin...as an anticancer agent, a therapeutic for Alzheimer's disease, a treatment for hangovers, erectile dysfunction, baldness, hirsutism, a fertility-boosting, and contraceptive extract, collectively establishing the properties expected of a panacea." Paradoxically, and of great relevance to traditional herbalists, the researchers did say: "Of course, we do not rule out the possibility that an extract of crude turmeric might have beneficial effects on human health. The large residual complexity of natural product extracts, and even of refined natural product preparations, makes the identification of the active constituent(s) and evaluation of their efficacy in humans very difficult. Considering the overwhelming evidence showing the weakness of isolated curcumin (almost always a mixture of curcuminoids) as a viable therapeutic, consideration of holistic approaches that take into account the chemical and pharmacodynamics/ pharmacokinetics complexity of turmeric and its broad traditional medicines/nutritional foundation appears to be superior directions for future research in the turmeric domain. In addition, there is increasing evidence that traditional medicine agents cannot be adequately described with reductionist pharmacology models but require consideration of polypharmacology and synergy."<sup>38</sup>

It is for these reasons that this monograph will focus on whole herb studies as opposed to the overwhelming amount of curcumin studies.

In relation to this a July 2013 review identified numerous chemical entities from turmeric other than curcumin. The review states that it is unclear whether all of the activities ascribed to turmeric are due to curcumin or whether other compounds in turmeric can manifest these activities uniquely, additively or synergistically with curcumin. Studies have indicated that turmeric oil, present in turmeric, can enhance the bioavailability of curcumin. Over the past decade studies have indicated that curcumin-free turmeric (CFT) components possess numerous biological activities including anti-inflammatory, anticancer and antidiabetic activities. Elemene derived from turmeric is approved in China for the treatment of cancer. The review focuses on the

anticancer and anti-inflammatory activities exhibited by CFT and by some individual components of turmeric, including turmerin, turmerone, elemene, furanodiene, curdione, bisacurone, cyclocurcumin, calebin A and germacrone.<sup>39</sup>

This is a lesson to herbalists not to be reductionist when it comes to their herbs. Traditional herbal medicine is based on the premise that the medicinal activity of herbal products is not due to a single chemical but the combined effect of all its constituents. Even in today's highly sophisticated and technically advanced scientific world, many of these constituents or chemical compounds are still unidentified. However, when extracted in a balanced way, the synergistic activity of all the constituents allows the key compounds to work effectively. The biochemical equilibrium within the herb must be maintained as this has proven effective throughout the ages to both heal bodies and sustain good health. The active ingredient can lose its impact, or become less safe, if used in isolation from the rest of the plant. The effect of the whole plant is greater than its parts.<sup>40</sup>

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Keeping in mind the above information, and the interpretation of experimental studies, here is a summary of curcumin and curcuminoids. To date more than 65 (in 2017 it's 120)<sup>41</sup> human clinical trials of curcumin, which included more than 1000 patients, have been completed.<sup>42</sup> Extensive research over the past half century

has shown that at a molecular level curcumin (diferuloylmethane) can modulate multiple cell signalling pathways including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (NF-kappaB, TNF, IL-6, IL-1, COX-2, and 5-LOX). These clinical trials have addressed the pharmacokinetics, safety and efficacy of this nutraceutical against numerous diseases in humans. Some promising effects have been observed in patients with various pro-inflammatory diseases including cancer, cardiovascular disease, arthritis, Alzheimer's disease, psoriasis, uveitis (inflammation of the uvea in the eye), ulcerative proctitis, Crohn's disease, ulcerative colitis, irritable bowel disease, tropical pancreatitis, peptic ulcer, gastric ulcer, idiopathic orbital inflammatory pseudotumour, oral lichen planus, gastric inflammation, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, diabetic nephropathy, diabetic microangiopathy, lupus nephritis, renal conditions, acquired immunodeficiency syndrome, beta-thalassemia, biliary dyskinesia, Dejerine-Sottas disease, cholecystitis and chronic bacterial prostatitis. Curcumin has also shown protection against hepatic conditions, chronic arsenic exposure and alcohol intoxication. In clinical trials, curcumin has been used either alone or in combination with other agents. Various formulations of curcumin, including nanoparticles, liposomal encapsulation, emulsions, capsules, tablets and powder have been examined. Interestingly, 6-gingerol, a natural analogue of curcumin derived from the root of ginger (*Zingiber officinalis*), exhibits a biologic activity profile similar to that of curcumin.<sup>43,44</sup>

### Anti-inflammatory Activity

Inflammation, in particular chronic inflammation, has been associated with numerous human chronic diseases including cardiovascular, pulmonary, autoimmune and degenerative diseases such as cancer and diabetes.<sup>45</sup> Turmeric is widely used for the treatment of disorders associated with inflammation.

The results of a 2017 study suggest a preventive therapeutic potential for turmeric, and its

constituent curcumin, on inflammatory cells and oxidative stress in asthma. The study indicated a preventive effect on differential white blood cell, serum levels of nitric oxide 2, nitric oxide 3, malondialdehyde, catalase and thiol group of an *in vivo* model of asthma which is comparable to the effect of dexamethasone (a corticosteroid used to treat asthma) at used concentrations.<sup>46</sup>

A 2016 meta-analysis of randomised clinical trials using turmeric and its curcumin-enriched extracts for treating joint arthritis found relevant scientific evidence for the efficacy of turmeric as a therapeutic option in arthritis but concluded that more studies are necessary in order to definitively pin it down.<sup>47</sup>

A 2016 randomised, double-blind, placebo-controlled trial in 160 patients with osteoarthritis of the knee found that on chronic administration turmeric suppresses inflammation, brings about clinical improvement in patients and decreases oxidative stress. Over all significant improvement was observed in the patients who took turmeric as compared to placebo group.<sup>48</sup>

A 2013 randomised, single blind, placebo-controlled trial has demonstrated the safety and efficacy of turmeric as a useful treatment option for patients with primary painful knee osteoarthritis (OA). The study showed a significant decrease in the use of rescue medication (Paracetamol), which demonstrated turmeric's analgesic potential, along with clinical and subjective improvement, compared to placebo, over a period of 42 days. It was published in *Inflammopharmacology*, an international journal that concentrates on the mechanisms of action and the use of anti-inflammatory agents. The anti-inflammatory activity of curcuminoids from turmeric is well known however its polysaccharide fraction has not been evaluated until recently. Natural Remedies Private Limited, a supplier of standardised botanical extracts, recently developed a polysaccharide rich, water soluble extract named Turmacin (NR-INF-02), a novel extract of turmeric devoid of curcuminoids. In order to evaluate the safety and efficacy of this extract researchers from St. John's Medical College, Bangalore conducted the trial. A total of 120 patients (37 males and 83 females) with primary knee OA received either placebo (400mg twice daily) or Turmacin (500mg twice daily) or glucosamine sulphate (GS) (750mg

twice daily) alone or combination of Turmacin and GS for 42 days. The efficacy was assessed during the treatment period, on day 21 and day 42. The decrease in severity of pain symptom, and function of affected knee, as primary efficacy outcome measure was assessed using internationally validated methods including Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, respectively. The clinical examination of affected joint was measured by an orthopaedic specialist and using a Clinician Global Impression Change (CGIC) scale. The analysis of post-treatment scores following administration of Turmacin using VAS, WOMAC, and CGIC at each clinical visit showed a significant decrease ( $p < 0.05$  meaning the probability of that happening was less than 1 in 50) compared to placebo. The tolerability and acceptability profile of Turmacin was better during the trial period. This study effectively demonstrated the efficacy of Turmacin for overall joint health as assessed by joint crepitation or popping (37%), joint tenderness (86.2%), joint effusion (100%) and joint movement (83.3%).<sup>49</sup>

Another 2013 study to assess the effects of a herbal supplement on systemic inflammation and antioxidant status in non-dialysis chronic kidney disease (CKD) patients has shown that turmeric and *Boswellia serrata* are safe and tolerable, and helped to improve the levels of an inflammatory cytokine. CKD is characterised by a continuous reduction in kidney function, increased inflammation, and reduced antioxidant capacity. Sixteen patients with CKD were randomly chosen to receive a herbal supplement composed of turmeric and *Boswellia serrata*, or placebo. Plasma levels of interleukin-6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), glutathione peroxidase (GPx), and serum C-reactive protein (CRP) were measured at baseline and eight weeks. Baseline data demonstrated elevated inflammation and low antioxidant levels. A statistically significant anti-inflammatory effect was observed for IL-6.<sup>50</sup>

Lupus nephritis is an inflammation of the kidney caused by systemic lupus erythematosus, a disease of the immune system. The disease is responsive to immunosuppressive and steroid therapy but sometimes the disease relapses. A randomised and placebo-controlled study investigated the effects

of oral turmeric supplementation on 24 patients with relapsing or refractory biopsy proven lupus nephritis. With each meal, each patient in the trial group received one capsule for three months, which contained 500mg turmeric, of which 22.1mg was the active ingredient curcumin (3 capsules daily). The control group received 3 capsules (1 with each meal) for the same period, which contained starch and were identical in colour and size to capsules given to patients in the trial group. A significant decrease in proteinuria was found in the trial group compared with the control group. Also, systolic blood pressure and haematuria were significantly lower in the trial group after supplementation. The authors concluded that short-term turmeric supplementation can decrease proteinuria, haematuria and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis and can be used as an adjuvant safe therapy for such patients.<sup>51</sup>

Turmeric can be used as an adjunct to mechanical means in preventing and treating gingivitis. These were the findings of a 2016 comprehensive review to summarize and evaluate the evidence on the efficacy of turmeric as compared to chlorhexidine (a germicidal mouthwash for removing bacteria) in the prevention and treatment of gingivitis. Five reviewed studies show that both turmeric and chlorhexidine significantly decrease plaque index, and gingival index, and can therefore be used in the prevention and treatment of gingivitis. Gingivitis affects an estimated 80% of the population, and is characterized as the world's most predominant inflammatory periodontal disease. Without intervention gingivitis can advance to alveolar bone loss. Therefore the primary goal in patients suffering with gingivitis is to control plaque build-up and soft tissue inflammation. Current guidelines consider chlorhexidine as the gold standard in the prevention and treatment of gingivitis. However negative side effects of chlorhexidine, including oral mucosal erosion, discoloration of teeth and bitter taste, provide an opportunity for alternative medications. Turmeric possesses anti-inflammatory, antioxidant, antibacterial, antiviral, and antifungal properties. By virtue of these properties multiple controlled trials have been performed to investigate the efficacy of turmeric in gingivitis. However trials longer than 21 days with a greater number of patients are necessary to further evaluate the comparison

between turmeric and chlorhexidine.<sup>52</sup>

A 2015 randomised controlled clinical trial found that turmeric gel reported better acceptance than chlorhexidine gel for gingivitis. This was due to turmeric having a pleasant odour and no staining of teeth in comparison to that reported for the chlorhexidine gel which had a bitter taste and caused staining of teeth. Sixty patients with plaque-induced gingivitis were divided into two groups, Group A was given turmeric gel and Group B was given chlorhexidine gel for 21 days in vaccupress trays.<sup>53</sup>

A recent study in India compared the effects of experimental local-drug delivery system containing 2% whole turmeric (gel form) as an adjunct to scaling and root planning (SRP) with the effects observed using SRP alone. SRP is also known as conventional periodontal therapy, non-surgical periodontal therapy, or deep cleaning, and is the process of removing and/or eliminating the etiologic agents – dental plaque, its products, and calculus – which cause inflammation, thus helping to establish a periodontium that is free of disease. Thirty subjects with chronic localised or generalised periodontitis with pocket depth of 5 to 7mm were selected for the study. Control sites received SRP alone, while experimental sites received SRP plus 2% whole turmeric gel for seven days. Both groups demonstrated statistically significant reduction in the biomarkers of periodontitis. However a greater reduction was seen in all the parameters in the experimental group in comparison to the control group. The authors of the study concluded that whole turmeric gel can be effectively used as an adjunct to SRP and that whole turmeric is more effective than SRP alone in the treatment of periodontitis.<sup>54</sup>

The results of a 2017 study suggest a preventive therapeutic potential for turmeric, and its constituent curcumin, on inflammatory cells and oxidative stress in asthma. The study indicated a preventive effect on differential white blood cell, serum levels of nitric oxide 2, nitric oxide 3, malondialdehyde, catalase and thiol group of an *in vivo* model of asthma which is comparable to the effect of dexamethasone (a corticosteroid used to treat asthma) at used concentrations.<sup>55</sup>

Research over the past several years using animal

models has indicated that turmeric can act as an anti-inflammatory agent by modulating the expression of inflammatory molecules.<sup>56</sup>

The immune-stimulatory and anti-inflammatory activities of a turmeric extract (Turmacin) and its polysaccharide fraction were studied in 2013. Its effects on proliferation, nitric oxide, monocyte chemotactic protein-1, interleukins (ILs) and prostaglandin (PGE2) levels were determined *in vitro*. The findings revealed the novel anti-inflammatory property of the extract and its polysaccharide fraction by inhibiting the secretion of IL-12 and PGE2 *in vitro*.<sup>57</sup>

The administration of turmeric extract arrested the degenerative changes in the bone and joints of collagen-induced arthritic rats.<sup>58</sup> A study to determine the antiarthritic efficacy and mechanism of action of a well-characterised turmeric extract using a rat model of rheumatoid arthritis has demonstrated *in vivo* efficacy and identified a mechanism of action for the extract that supports further clinical evaluation of turmeric dietary supplements in the treatment of rheumatoid arthritis. The extract profoundly inhibited joint inflammation and periarticular joint destruction in a dose-dependent manner. It also prevented local activation of NF-kappaB and the subsequent expression of NF-kappaB-regulated genes mediating joint inflammation and destruction, including chemokines, cyclooxygenase 2 and receptor activator of nuclear factor kappa B ligand (RANKL). Consistent with these findings, inflammatory cell influx, joint levels of prostaglandin E(2) and periarticular osteoclast formation were inhibited by turmeric extract treatment.<sup>59</sup>

Turmeric was shown to possess anti-inflammatory properties *in vivo*. Turmeric exhibited its activity by reducing the aggregation of inflammatory cells surrounding the hepatic bile ducts, which correlates with a decreased serum alanine transaminase level. The decrease in direct bilirubin levels in the animals treated with turmeric suggests that turmeric may enhance biliary contraction. The study found that turmeric clearly reduces the inflammatory cells in induced parasitic disease at an early stage. This finding may be connected with a reduction in the risk factors of bile duct cancer development.<sup>60</sup>

Turmeric plays a protective role in the development

of acute pancreatitis and pancreatitis-associated lung injury a recent study has shown. The effects of turmeric on induced acute pancreatitis were studied *in vivo*. The oral administration of turmeric significantly ameliorated the severity of pancreatitis and pancreatitis-associated lung injury, as was shown by the reduction in pancreatic oedema, neutrophil infiltration, vacuolization, necrosis, serum amylase, lipase and cytokine levels and mRNA expression of multiple inflammatory mediators such as interleukin (IL)-1 $\beta$  and -6 and tumour necrosis factor (TNF)- $\alpha$ . In order to identify the regulatory mechanism of turmeric on induced pancreatitis, the authors examined the level of haeme oxygenase HO-1 in the pancreas. They found that the administration of turmeric induced HO-1.<sup>61</sup>

A study of the effect of turmeric extracts on inflammatory mediator production has shown that organic extracts of turmeric exhibited cytotoxicity and inhibited production of lipopolysaccharide induced tumour necrosis factor alpha and prostaglandin E2 in human leukaemia cells.<sup>62</sup>

#### **Antioxidant Activity**

There are a number of *in vitro* studies demonstrating turmeric acting as a free radical scavenger. A 2006 study found that in addition to curcumin, turmeric contains the antioxidants protocatechic acid and ferulic acid. Further, turmeric also exhibited significant protection to DNA against oxidative damage as evidenced by migration of DNA on the agarose gel (A principal component of agar, agarose is frequently used in molecular biology for the separation of large molecules, especially DNA).<sup>63</sup>

An aqueous extract of turmeric has been shown to have significant antioxidant activity. Liposomal lipid peroxidation and peroxide induced DNA damage were investigated. Inhibition of lipid peroxidation was studied using 400 microM uric acid, beta-carotene, alpha-tocopherol, curcumin and butylated hydroxyanisole (BHA). Curcumin was as effective an antioxidant as BHA. An aqueous extract of turmeric was also found to be an effective inhibitor. The inhibition obtained using this aqueous extract, incorporated into the liposome itself, was 70% at 300 ng/microlitre. This indicates the presence of yet another antioxidant in turmeric besides the lipophilic curcumin. The aqueous antioxidant extended 80% protection to DNA against peroxidative injury

at 100ng/microlitre. This component of turmeric is being characterised and investigated as an antioxidant/anticlastogen and as an antipromoter.<sup>64</sup>

Another *in vitro* study provides evidence that turmeric gives protection against oxidative stress induced by hydrogen peroxide in a renal cell line.<sup>65</sup> Another *in vitro* assay of all fractions of a turmeric extract preparation exhibited pronounced antioxidant activity, which was assigned to the presence of curcumin and other polyphenols.<sup>66</sup> Consumption of an aqueous turmeric extract exhibited hypolipidaemic and antioxidant activities in a hypercholesterolaemic zebrafish model and potently suppressed the incidence of atherosclerosis via its strong antioxidant potential.<sup>67</sup>

One of the most important effects of thyroid hormones (T3 and T4) is the elevation of mitochondrial respiration, producing a hyper-metabolic state with excess generation of free radicals. It has been shown that tissues in hyperthyroid rats exhibit low antioxidant capacity and high susceptibility to oxidative challenge. Oxidative stress from superoxide (O<sub>2</sub><sup>-</sup>) and other reactive oxygen species (ROS) contributes to the development of renal insufficiency and in the pathogenesis of renal diseases, producing vascular, glomerular, tubular and interstitial injury. Thyroxine has been reported to induce renal hypertrophy with a rise in the DNA content. However, there is a paucity of information on T3-induced oxidative damage to mammalian kidney in general and with respect to antioxidant treatment in particular. With this background an investigation was designed to compare the effectiveness of turmeric and its active principle curcumin on T3-induced oxidative stress and hyperplasia in rat kidney. The study showed that turmeric exhibited better potential in comparison to curcumin in reversing thyroid hormone (T3) induced oxidative stress and hyperplasia in rats. It was hypothesised that regulation of cell cycle in rat kidney by T(3) is via reactive oxygen species and curcumin reverses the changes by scavenging them. Although the response trends are comparable for both turmeric and curcumin, the magnitude of alteration is more in the latter. The researchers concluded that turmeric in the current dose schedule is a safer bet than curcumin in normalizing the T(3)-induced hyperplasia which may be due to the lower concentration of the active principle in the

whole spice.<sup>68</sup>

### Anticancer Activity

Turmeric has been most widely investigated for its anticancer activity and has exhibited it in human subjects. The most common cancer types in which turmeric has shown potential are those of the liver, breast, mouth and stomach. For several years (in 2017) curcumin has been at the centre of interest for scientific studies in the field of cancer treatment. Laboratory studies have presented some favourable results in terms of curcumin's antioxidant, anti-inflammatory and anticancer properties in particular. However, since such findings have yet to be confirmed in clinical studies, its effect on humans is not clearly known.<sup>69</sup>

In spite of major advances in oncology the World Health Organization predicts that cancer incidence will double within the next two decades. Although it is well understood that cancer is a hyperproliferative disorder mediated through dysregulation of multiple cell signalling pathways, most cancer drug development remains focused on modulation of specific targets, mostly one at a time, with agents referred to as 'targeted therapies', 'smart drugs' or 'magic bullets'. How many cancer targets there are is not known and how many targets must be attacked to control cancer growth is not well understood. Although more than 90% of cancer-linked deaths are due to metastasis of the tumour to vital organs, most drug targeting is focused on killing the primary tumour. Besides lacking specificity the targeted drugs induce toxicity and side effects that sometimes are greater problems than the disease itself. Furthermore the cost of some of these drugs is so high that most people cannot afford them. Turmeric has potential anticancer properties and is known for its safety and low cost. It can selectively modulate multiple cell signalling pathways linked to inflammation and to survival, growth, invasion, angiogenesis and metastasis of cancer cells.<sup>70</sup>

Turmeric may have potential therapeutic activity against human colon cancer a 2015 *in vitro* study found. Turmeric potently inhibited the growth of all human colon cancer cell lines tested in a dose- and time-dependent manner.<sup>71</sup>

Nitric oxide (NO) is involved in different stages of malignancies. Increased levels of NO have been reported in different leukaemias, including chronic

myeloid leukaemia (CML) for which imatinib is the preferred drug for treatment. A 2012 study evaluated the effects of turmeric powder in reducing NO levels in 50 CML patients. The CML patients were divided into two groups, group A receiving imatinib (400mg twice a day) alone and group B receiving turmeric powder (5g three times/day dissolved in 150mL of milk) along with imatinib (400mg twice a day) for six weeks. Nitric oxide levels were estimated in these patients before and after receiving therapy. Nitric oxide levels were found to be significantly decreased in both the groups, but more significantly in group B after receiving the respective treatments. The authors concluded that turmeric acts as an adjuvant to imatinib in decreasing the NO levels and may help in the treatment of CML patients.<sup>72</sup>

The incidence of cancer is significantly lower in regions where turmeric is heavily consumed. Lower cancer incidence attributed to turmeric was investigated by examining its effects on tumour cell proliferation, on pro-inflammatory transcription factors NF- $\kappa$ B and transcription factor 3 (STAT3), and on associated gene products. Turmeric is more potent in inhibiting colorectal cancer growth in comparison to curcumin using cell based studies as reported recently. Turmeric inhibited NF- $\kappa$ B activation and down-regulated NF- $\kappa$ B-regulated gene products linked to survival (Bcl-2, cFLIP, XIAP, and cIAP1), proliferation (cyclin D1 and c-Myc), and metastasis (CXCR4) of cancer cells. The spice suppressed the activation of STAT3, and induced the death receptors (DR)4 and DR5. Turmeric enhanced the production of ROS, and suppressed the growth of tumour cell lines. Furthermore, turmeric sensitised the tumour cells to chemotherapeutic agents capecitabine and taxol. Turmeric was found to be more potent than pure curcumin for cell growth inhibition. Turmeric also inhibited NF- $\kappa$ B activation induced by RANKL that correlated with the suppression of osteoclastogenesis (the development of osteoclasts, which are large multinucleate bone cells which absorb bone tissue during growth and healing, from blood cells specifically from monocytes/macrophages). The results indicated that turmeric can effectively block the proliferation of tumour cells through the suppression of NF- $\kappa$ B and STAT3 pathways.<sup>73</sup>

An ethanolic extract of turmeric was found to

produce remarkable symptomatic relief in patients 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.<sup>74</sup>

Turmeric extract offered protection against induced increases in micronuclei in circulating lymphocytes of healthy patients. In subsequent studies patients suffering from oral submucous fibrosis (a highly potent pre-cancerous disease of the oral cavity mainly caused by chewing betel nut or tobacco) were given a total oral dose of 3g turmeric extract a day as a control for three months. Turmeric extract decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes.<sup>75</sup>

The superior toxicity of turmeric, in comparison to curcumin, against pancreatic cancer cells was shown in a study investigating the cytotoxic effects of turmeric force (TF), a supercritical and hydroethanolic extract of turmeric, alone and in combination with gemcitabine in two pancreatic carcinoma cell lines. Gemcitabine is a first line cancer drug widely used for the treatment of pancreatic cancer however its therapeutic efficiency is significantly limited by resistance of pancreatic cancer cells to this and other chemotherapeutic drugs. TF was highly cytotoxic to the cell lines and had cytotoxicity superior to that of curcumin. The combination of gemcitabine and TF was synergistic with IC90 levels achieved in both pancreatic cancer cell lines at lower concentrations than for either agent alone. The synergistic effect was associated with an increased inhibitory effect of the combination on nuclear factor-kappaB activity and signal transducers and activators of STAT3 activities as compared to the single agent.<sup>76</sup>

Other studies using rat models have shown the potential of turmeric against hepatocarcinogenesis and liver carcinogenesis.<sup>77,78</sup> Hamster studies have shown that turmeric exhibits activity against oral carcinogenesis.<sup>79</sup>

A recent *in vitro* study has shown an ethanolic extract of turmeric can down-regulate a protein molecule (SIRT1) involved in longevity and diverse

metabolic processes, including cancer.<sup>80</sup>

### Antiproliferative Activity

Studies over the past several years have indicated the growth inhibitory effects of turmeric against numerous cancer cells.

A 2013 *in vitro* study indicates that the use of turmeric extract might be a safer approach to finding a lasting cure for acute monocytic leukaemia (AML M5 or AMoL). AMoL is one of the several types of leukaemia that are still awaiting cures. The use of chemotherapy for cancer management can be harmful to normal cells in the vicinity of the target leukaemia cells. This study assessed the potency of the extracts from lesser galangal, turmeric, and ginger against AML M5 to use the suitable fractions in nutraceuticals. Aqueous and organic solvent extracts from the leaves and rhizomes of lesser galangal and turmeric, and from the rhizomes only of ginger were examined for their antiproliferative activities against AMoL cells *in vitro*. Lesser galangal leaf extracts in organic solvents of methanol, chloroform, and dichloromethane maintained distinctive antiproliferative activities over a 48 hour period. The turmeric leaf and rhizome extracts and ginger rhizome extracts in methanol also showed distinctive anticancer activities. Further investigations will be required to establish the discriminatory tolerance of normal cells to these extracts, and to identify the compounds in these extracts that possess the antiproliferative activities.<sup>81</sup>

Turmeric extract inhibited cell growth *in vitro* at a concentration of 0.4mg/mL and was cytotoxic to lymphocytes and Dalton's lymphoma cells at the same concentration when the anticancer activity of the rhizomes of turmeric were evaluated. Initial experiments indicated that turmeric extract and curcumin reduced the development of animal tumours.<sup>82</sup>

### Chemoprevention Activity

An *in vivo* study designed to seek the chemopreventive effects of turmeric and its mechanisms suggests that it can have beneficial effects on the early and late stages of liver pathogenesis, preventing and delaying liver carcinogenesis in mice. Unlike other forms of hepatocellular carcinoma, hepatocellular carcinoma

induced by hepatitis B virus infection shows a poor prognosis after conventional therapies. Hepatitis B virus induces liver cirrhosis and hepatocellular carcinoma. Many researchers have made efforts to find new substances that suppress the activity of hepatitis B virus. Turmeric mixture concentrated with dextrose water by boiling was lyophilised. Turmeric treated mice showed less visceral fat, a smaller liver/body weight ratio and delayed liver pathogenesis. The authors suggest that turmeric should be considered as a potential chemopreventive agent for hepatitis B virus -related hepatocarcinogenesis.<sup>83</sup>

The modulating effects of turmeric, ethanolic turmeric extract and curcumin-free aqueous turmeric extract on the initiation or post-initiation phases of DMBA-induced mammary tumourigenesis were investigated in rats. The data clearly indicated that dietary administration of turmeric and ethanolic turmeric extract showed strong chemopreventive activity during initiation as well as post-initiation phases of DMBA-induced rat mammary tumourigenesis.<sup>84</sup>

A study aimed at assessing the potential chemopreventive effects of turmeric in hepatocarcinogenic rats has shown that dietary supplementation of turmeric delayed the initiation of carcinogenesis.<sup>85</sup>

Turmeric was shown to inhibit promotion of lymphoma cells induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in *in vitro* studies evaluating natural products as potential cancer chemopreventive agents.<sup>86</sup>

#### **Antimutagenic Activity**

A study on the antimutagenic effects of turmeric were assessed in 16 chronic smokers. It was observed that turmeric, given in doses of 1.5g/day for 30 days, significantly reduced the urinary excretion of mutagens in smokers. In contrast, in six non-smokers, who served as control, there was no change in the urinary excretion of mutagens after 30 days. These results indicate that dietary turmeric is an effective antimutagen and it may be useful in chemoprevention. Randomised, placebo controlled studies are required to confirm these findings.<sup>87</sup>

Turmeric has been shown to inhibit chemical carcinogenesis. Curcumin free aqueous turmeric, and to a lesser degree ethanolic turmeric extract

and turmeric powder, have the potential to suppress benzo(a)pyrene-induced forestomach tumours in mice.<sup>88</sup>

In a similar study, the antitumour activity of turmeric was investigated in mice by comparing the activities of an aqueous turmeric extract and its constituents, a curcumin-free aqueous turmeric extract and curcumin on chemical carcinogenesis. Both the aqueous extract and the curcumin-free extract dose dependently exhibited antimutagenic activity against bacteria. Furthermore, the incidence and multiplicity of forestomach tumours induced by benzo [alpha] pyrene in the mice were significantly inhibited.<sup>89</sup>

In an *in vitro* study, turmeric was shown to be as effective as rosemary in decreasing the levels of heterocyclic amines (mutagenic compounds formed when foods are cooked at high temperatures) in fried beef patties.<sup>90</sup>

#### **Immunomodulatory Activity**

A recent *in vitro* study using hot water turmeric extract has shown that it exhibits immune stimulatory activities in human peripheral blood mononuclear cells. The findings revealed the potential use of turmeric crude extract as an adjuvant supplement for cancer patients, whose immune activities were suppressed during chemotherapies.<sup>91</sup>

#### **Radioprotective Activity**

A study investigated the effect of an aqueous extract of turmeric on the sensitivity of *Escherichia coli*, *Bacillus megaterium* and *Bacillus pumilus* spores to gamma radiation. The extract offered protection to these organisms against inactivation by gamma-radiation. The study indicated the importance of turmeric, among ingredients in food, as a dose-modifying factor during radiation processing.<sup>92</sup> Another study investigated the possible role of crude turmeric extracts in radioprotection by a variety of methods. This study revealed that dimethyl sulfoxide extracts of turmeric produced a significant amount of radioprotection, which is very similar in nature and extent to that imparted by curcumin. Turmeric also clearly showed protection against X-ray induced DNA damage of *E. coli* cells.<sup>93</sup>

### Antiaging and Neuroprotective Activity

Main pharmacological properties of turmeric: The cognitive deficits in the brain aging process are due to inflammatory, oxidative stress and the apoptotic process. Interestingly, the beneficial effects of turmeric on the aging brain are caused by anti-inflammatory, antioxidant and antiapoptotic pharmacological properties.<sup>94</sup>

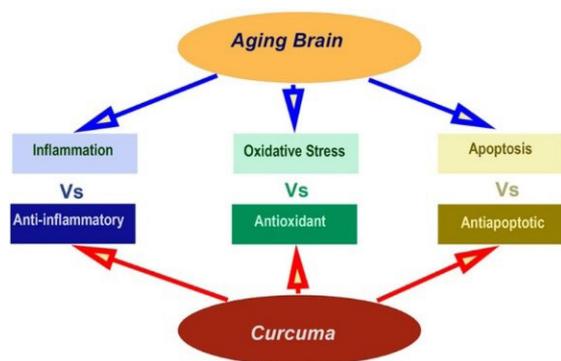


Photo credit: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5514855/figure/F1/>

Several reports suggest that the anti-inflammatory, antioxidant and antiapoptotic pharmacological properties of turmeric may be beneficial in the brain aging process. Animal models of aging have roundly demonstrated the biochemical and morphological effects of turmeric on the prefrontal cortex and hippocampus which are the regions involved in the memory and learning process. Consequentially the effects of turmeric on the processes of memory involve an improvement in the interneuronal communication of both regions. Accordingly turmeric should be considered as a therapeutic alternative in the control of the aging process with the main aim of improving the quality of life of elderly people.<sup>95</sup>

Turmeric has shown neuroprotective properties and has been reported to prevent aging and improve memory. While the mechanism(s) underlying these effects are unclear, they may be related to increases in neural plasticity. Morphological changes have been reported in neuronal dendrites in the limbic system in animals and elderly humans with cognitive impairment. In this regard there is a need to use alternative therapies that delay the onset of morphologies and behavioural characteristics

of aging. Therefore the objective of a 2017 study was to evaluate the effect of turmeric on cognitive processes and dendritic morphology of neurons in the prefrontal cortex, the CA1 and CA3 regions of the dorsal hippocampus, the dentate gyrus and the basolateral amygdala of aged rats. 18-month-old rats were administered turmeric (100 mg/kg) daily for 60 days. After treatment, recognition memory was assessed. Turmeric treated rats showed a significant increase in the exploration quotient. The preservation of dendritic morphology was positively correlated with cognitive improvements. The results suggest that turmeric induces modification of dendritic morphology in the aforementioned regions. These changes may explain how turmeric slows the aging process that has already begun in these animals, preventing deterioration in neuronal morphology of the limbic system and recognition memory.<sup>96</sup>

Turmeric may be useful in the treatment of Parkinson's disease a 2017 *in vitro* study found. Parkinson's disease is a degenerative disorder of the central nervous system that affects the motor system of the brain. Death of dopamine-producing cells in the substantia nigra leads to the disease. Exposure to salsolinol, which is an endogenous neurotoxin, has been associated with damage to dopamine-producing cells. The study assessed the toxicity of salsolinol in human neuroblastoma cells and subsequently investigated the neuroprotective potential of turmeric in salsolinol-induced toxic conditions in those cells.<sup>97</sup>

Multiple pathways, including oxidative stress and mitochondrial damage, are implicated in neurodegeneration during Parkinson's disease. The current Parkinson's disease drugs provide only symptomatic relief and have limitations in terms of adverse effects and inability to prevent neurodegeneration. Therefore, there is a demand for novel compound(s)/products that could target multiple pathways and protect the dying midbrain dopaminergic neurons, with potential utility as adjunctive therapy along with conventional drugs. To explore the neuroprotective property of turmeric in Parkinson's disease, mice were subjected to dietary supplementation with aqueous suspensions of turmeric for three months, mimicking its chronic consumption and challenged *in vivo* with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It was

found that chronic dietary consumption of turmeric protects the brain against neurotoxic insults, with potential application in neurodegeneration.<sup>98</sup>

Oxidative damage in the hippocampus can induce the apoptosis of neurons associated with the pathogenesis of dementia. The aim of a 2017 study was to reveal the possible antiapoptotic effect of turmeric on the hippocampal neurons of rats exposed to the neurotoxicant trimethyltin. The results showed that a 200 mg/kg bw dose of turmeric extract may exert antiapoptotic effect *in vivo*.<sup>99</sup>

The therapeutic potential of turmeric in Alzheimer's disease (AD) was reviewed in a 2012 Pakistani study. AD is the most common form of dementia. There is limited choice in modern therapeutics and drugs available have limited success, with multiple side effects, in addition to high cost. Hence, newer and alternate treatment options are being explored for effective and safer therapeutic targets to address AD. Turmeric possesses multiple medicinal uses including treatment for AD. As mentioned above in constituents, curcuminoids, a mixture of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, are vital constituents of turmeric. It is generally believed that curcumin is the most important constituent of the curcuminoid mixture that contributes to the pharmacological profile of parent curcuminoid mixture or turmeric. A careful literature study reveals that the other two constituents of the curcuminoid mixture also contribute significantly to the effectiveness of curcuminoids in AD. Therefore, it is emphasised in this review that each component of the curcuminoid mixture plays a distinct role in making the curcuminoid mixture useful in AD, and hence, the curcuminoid mixture represents turmeric in its medicinal value better than curcumin alone. The progress in understanding the disease aetiology demands a multiple-site-targeted therapy, and the curcuminoid mixture of all components, each with different merits, makes this mixture more promising in combating the challenging disease.<sup>100</sup>

The findings of an *in vivo* study revealed that optimised turmeric extract HSS-888 represents an important step in botanical based therapies for Alzheimer's disease by inhibiting or improving plaque burden, Tau phosphorylation (characteristic feature of Alzheimer's disease) and microglial inflammation

leading to neuronal toxicity. In a previous *in vitro* study, the standardised turmeric extract, HSS-888, showed strong inhibition of beta amyloid aggregation and secretion *in vitro*, indicating that HSS-888 might be therapeutically important.<sup>101</sup>

An animal study has suggested enhanced learning ability, and spatial memory, after turmeric extract treatment.<sup>102</sup>

### **Gastrointestinal Activity**

The results of a 2014 study, when published, will help patients and healthcare practitioners to make informed decisions when considering turmeric as an alternative therapy for digestive disorders. Digestive disorders pose significant burdens to millions of people worldwide in terms of morbidity, mortality and healthcare costs. Turmeric has been traditionally used for conditions associated with the digestive system, and its therapeutic benefits were also confirmed in clinical studies. However, rigorous systematic review on this topic is severely limited. The study aims to systematically review the therapeutic and adverse effects of turmeric and its compounds on digestive disorders, including dyspepsia, peptic ulcer, irritable bowel disease, Crohn's disease, ulcerative colitis, and gastroesophageal reflux disease. The study will include both randomised controlled trials and non-randomised controlled trials assessing the efficacy and safety of turmeric or its compounds in comparison to a placebo or any other active interventions for digestive disorders without any restrictions on participant age or language of publication. The primary outcome is the proportion of patients that have experienced treatment success. Secondary outcomes are the prevalence of an individual symptom of digestive disorders, the proportion of patients who experienced relapse, the number of physician visits/hospitalization due to digestive disorders, health-related quality of life and the proportion of patients who experienced adverse events.<sup>103</sup>

### **Hepatoprotective Activity**

A 2013 clinical trial has shed light on turmeric's remarkable liver protective and regenerative properties. Previously, the hepatoprotective activity of turmeric and its constituents have been reported in the literature. Recent evidence has shown that

turmeric, or curcumin, can improve the liver function in rats with hepatic injury.<sup>104,105,106,107</sup> In view of the hepatoprotective and other beneficial effects of fermented turmeric powder (FTP) in animal models, a randomised, double-blind, placebo-controlled clinical trial was designed and conducted to evaluate the effects of 12-week FTP treatment on serum aminotransferase levels in subjects with elevated alanine transaminase (ALT) levels. The hypothesis tested was that FTP might improve liver function. Therefore, serum ALT levels was defined as the primary end point of the study. The trial was conducted between November 2010 and April 2012 at the clinical trial centre for functional foods of the Chonbuk National University Hospital, South Korea. The data from this trial indicates that FTP is effective and safe, generally well-tolerated without severe adverse effects (AEs), in the treatment of subjects with elevated ALT levels over a 12 weeks period. The FTP was crushed turmeric which had been fermented with 2% (wt/wt) of *Aspergillus oryzae* at 25°C for 36 h and dried. Fermented turmeric was standardised to 0.79mg curcumin per 1.0g powder. Average curcumin contents in non-fermented turmeric and FTP were approximately 2.0mg/g and 0.79mg/g, respectively. In this study, the subjects were not actively asked to change their lifestyle or to change their diet. The trial included 60 fsubjects, 20 years old and above, who were diagnosed with mild to moderate elevated ALT levels between 40IU/L and 200IU/L. Sixty subjects were randomised to receive FTP 3.0g per day or placebo 3.0g per day for 12 weeks. The treatment group received two capsules of FTP three times a day after meals, for 12 weeks. The primary efficacy endpoint was change in the ALT levels in the two groups. The secondary efficacy endpoints included its effect on aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TB), and lipid profiles. Safety was assessed throughout the study using ongoing laboratory tests. Sixty subjects were randomised in the study (30 into the FTP group, 30 into the placebo group), and among them, twelve subjects were excluded from the analysis for protocol violation, adverse events or consent withdrawal. The two groups did not differ in base line characteristics. After 12 weeks of treatment, 48 subjects were evaluated. Of the 48 subjects, 26 randomly received FTP capsules and 22 received

placebo. The FTP group showed a significant reduction in ALT levels after 12 weeks of treatment compared with the placebo group ( $p = .019$ ). It was also observed that the serum AST levels were significantly reduce in the FTP group than placebo group ( $p = .02$ ). The GGT levels showed a tendency to decrease, while the serum alkaline phosphatase (ALP), TB, and lipids levels were not modified. There were no reported severe AEs during this study, or abnormalities observed on blood glucose, total protein, albumin, blood urea nitrogen, and creatinine levels.<sup>108</sup>

The results of a 2017 study suggest that oral administration of a hot water extract of turmeric may have a protective effect against ethanol-induced liver injury by suppressing hepatic oxidation and inflammation, at least partly through the effects of bisacurone. Bisacurone, a component of turmeric extract, is known to have antioxidant activity and anti-inflammatory activity. Oxidative stress and inflammatory cytokines play an important role in ethanol-induced liver injury.<sup>109</sup>

### **Antiulcer Activity**

An open, pilot study (phase II clinical trial) on the effect of turmeric on healing peptic ulcers showed a satisfactory reduction in abdominal pain and discomfort in the first week of a four week treatment. Forty-five patients (24 men and 21 women, aged between 16-60 years) were included in the study. Of these, 25 patients (18 men and 7 women) underwent endoscopy for their ulcers located in the duodenal bulb and gastric angulus (the angulus being defined as the lowest point of the lesser curvature). The ulcer sizes varied between 0.5 to 1.5cm in diameter. Turmeric-filled capsules (crude powder of the dried rhizome) was given orally in the dose of two capsules (300mg each) five times daily, one half to an hour before meals, at 16.00 hours and at bedtime continuously. The result after four weeks of treatment showed that ulcers were absent in 12 cases (48%). Eighteen cases (72%) had no ulcers after eight weeks of treatment and 19 cases (76%) did not have ulcers after 12 weeks of treatment. The remaining 20 cases were not found to have ulcers and some did not undergo endoscopy. These 20 people appeared to have erosions, gastritis and dyspepsia, and turmeric capsules were given to these people for four weeks. The abdominal pain

and discomfort satisfactorily subsided in the first and second weeks. The authors concluded that turmeric has the capacity to heal peptic ulcers. To study the side effects of turmeric, blood chemistry and haematology were performed. All 54 patients had no significant changes in haematological system, liver and renal functions both before and after treatment. The authors wrote that many Thai people suffer from abdominal pain due to gastric and duodenal ulcers. Traditional doctors used pills Khamin Chan (Turmeric) powder mixed with honey to successfully cure their ailment. The authors were interested in proving the effects of turmeric on the epithelial mucosa of stomach and duodenum of peptic ulcer patients to see whether the healing of the ulcer in the mucosa by endoscopy corresponds to the disappearance of abdominal pain.<sup>110</sup>

An oral extract of turmeric was found to protect the gastric mucosal layer of pylorus ligated rats in a dose dependent manner and was as effective as ranitidine at higher doses of turmeric. Turmeric specifically inhibited gastric acid secretion by blocking H(2) histamine receptors in a competitive manner.<sup>111</sup>

#### **Irritable Bowel Syndrome Activity**

In a partially blinded, randomised, two-dose, pilot study it was shown that turmeric may help reduce irritable bowel syndrome (IBS) symptomology. The study was not placebo-controlled and the authors acknowledged that a placebo effect was likely to have contributed to positive results. Five hundred (500) volunteers were screened for IBS using the Rome II criteria. Two hundred and seven (207) suitable volunteers were randomised. One or two tablets of a standardised turmeric extract (72 or 144mg) were taken daily for eight weeks. A statistically significant reduction in IBS prevalence compared with baseline was seen in both treatment groups (53% and 60% with the 72mg and 144mg doses, respectively). A self-reported improvement in symptoms (67% and 70%) and increased quality of life (assessed by questionnaire) was also reported.<sup>112</sup> Another study hypothesised that turmeric in curry might increase bowel motility and activate hydrogen-producing bacterial flora in the colon, thereby increasing the concentration of breath hydrogen. Eight healthy subjects fasted for 12 hours and ingested curry and rice with or without turmeric. Breath-hydrogen concentrations

were analysed every 15 minutes for six hours by gas chromatography with a semiconductor detector. Curry with turmeric significantly increased the area under the curve of breath hydrogen and shortened small-bowel transit time, compared with curry not containing turmeric. These results suggested that dietary turmeric activated bowel motility and carbohydrate colonic fermentation.<sup>113</sup>

Turmeric may protect against inflammatory bowel disease (IBD) following the results of a 2016 *in vivo* study. The study investigated the protective effects of turmeric on induced colitis in rats. Turmeric improved body weight gain, mean macroscopic and microscopic ulcer scores in the rats. The increase in the mean serum glutathione level may help in the reduction of oxidative stress associated with IBD.<sup>114</sup>

#### **Dyspepsia Activity**

A multicentre, randomised, double-blind placebo-controlled trial investigating the efficacy of turmeric for treatment of dyspepsia and flatulence in 116 adult patients who had acid dyspepsia, flatulent dyspepsia or atonic dyspepsia found that 87% of patients receiving turmeric responded to the treatment compared to 53% receiving placebo. Each patient received two capsules of placebo or study drugs four times a day for a week. The differences in efficacy between placebo and active drugs were statistically significant and clinically important.<sup>115</sup>

#### **Chologogue and Hypolipidaemic Activity**

A recent animal study has found that turmeric may be considered a functional food for regulating plasma cholesterol levels and preventing the development of fatty liver in people who frequently consume a high-cholesterol diet. The results showed that rats fed a high-cholesterol diet supplemented with turmeric extract had a significant increase in high density lipoprotein (HDL) cholesterol and decreases in total plasma cholesterol and low density lipoprotein (LDL) cholesterol along with several other variables, showing that turmeric prevents hypercholesterolaemia and the formation of fatty liver by the modulation of expressions of enzymes that are important to cholesterol metabolism.<sup>116</sup>

#### **Antiatherogenic Activity**

Atherosclerosis is characterised by oxidative damage that affects lipoproteins, the walls of

blood vessels and subcellular membranes. The oxidation of LDL also plays an important role in its development.<sup>117</sup>

A study was done evaluating the effects of oral supplementation with a turmeric ethanol and aqueous extract on the susceptibility to oxidation of cellular, and subcellular, membranes affected in the atherosclerotic process, such as erythrocyte membranes and liver microsomes, in rabbits fed with a high-fat diet. The results show that turmeric inhibits erythrocyte and liver microsome membrane oxidation and may contribute to the prevention of effects caused by a diet high in fat and cholesterol in blood and liver during the development of atherosclerosis.<sup>118</sup> In another study oral administration of turmeric extract inhibited LDL oxidation and had hypocholesterolaemic effects in atherosclerotic rats.<sup>119</sup>

#### **Skin Health and Wound Healing Activity**

A 2016 systematic review was conducted to examine the evidence for the use of both topical and ingested turmeric or curcumin to modulate skin health and function. The PubMed and Embase databases were systematically searched for clinical studies involving humans that examined the relationship between products containing turmeric, curcumin and skin health. A total of 234 articles were uncovered and a total of 18 studies met inclusion criteria.

Nine studies evaluated the effects of ingestion, eight studies evaluated the effects of topical, and one study evaluated the effects of both ingested and topical application of turmeric or curcumin. Skin conditions examined include acne, alopecia, atopic dermatitis, facial photoaging, oral lichen planus, pruritus, psoriasis, radiodermatitis and vitiligo. Ten studies noted statistically significant improvement in skin disease severity in the turmeric or curcumin treatment groups compared with control groups. Overall, there is early evidence that turmeric and curcumin products and supplements, both oral and topical, may provide therapeutic benefits for skin health. However, currently published studies are limited and further studies will be essential to better evaluate efficacy and the mechanisms involved.<sup>120</sup>

The clinical and therapeutic benefit of a turmeric extract microemulgel topical formulation was

evaluated on 34 patients with mild to moderate plaque psoriasis in a randomised, prospective intra-individual, right-left comparative, placebo-controlled, double-blind 2015 clinical trial. Plaque psoriasis is an autoimmune, inflammatory skin disorder that causes patches of inflamed, thickened skin lesions. The results show that the clinical and quality of life parameters in treated lesions in comparison with untreated lesions have improved. Based on these findings the authors proposed the microemulgel (which contained 0.5% of turmeric extracted with water and alcohol used twice daily) may well be considered as an alternative in some patients and most likely as an add-on therapeutic option for many patients suffering with plaque psoriasis.<sup>121</sup>

Psoriasis is a chronic inflammatory skin disorder characterised by rapid proliferation of keratinocytes and incomplete keratinisation. Discovery of safer and more effective antipsoriatic drugs remains an area of active research. An ethanolic extract of turmeric has been shown to possess antipsoriatic activity in a keratinocyte cell line in an *in vitro* model. Turmeric significantly decreased the expression of colony stimulating factor (CSF)-1, interleukin (IL)-8, NF-κB2, NF-κB1. The study suggested that turmeric might exert its activity by controlling the expression of NF-κB signalling biomarkers.<sup>122</sup>

The potential efficacy of fresh turmeric paste to heal wounds was tested in a preclinical animal study. Turmeric paste was compared with honey as a topical medicament against a control on experimentally created full-thickness circular wounds in 18 rabbits. Wound healing was assessed on the basis of physical, histomorphological, and histochemical parameters on treatment days 0, 3, 7, and 14. Only tensile strength was measured on day 14 of treatment. It was observed that the wound healing was statistically significantly faster in both treatment groups compared to the control group.<sup>123</sup>

A study aiming to clarify whether turmeric prevents chronic ultraviolet B (UVB)-irradiated skin damage in mice has had positive results. The effects of a turmeric extract on skin damage including changes in skin thickness and elasticity, pigmentation and wrinkling caused by long-term, low-dose ultraviolet B irradiation in melanin-possessing hairless mice were studied. The extract (at 300 or 1000mg/kg,

twice daily) prevented an increase in skin thickness and a reduction in skin elasticity induced by chronic UVB exposure. It also prevented the formation of wrinkles and melanin (at 1000mg/kg, twice daily) as well as increases in the diameter and length of skin blood vessels and in the expression of matrix metalloproteinase-2 (MMP-2). Prevention of UVB-induced skin aging by turmeric may be due to the inhibition of increases in MMP-2 expression caused by chronic irradiation.<sup>124</sup>

### **Analgesic Activity**

A double-blind randomised placebo-controlled study found turmeric improved postoperative pain and fatigue in 50 patients following laparoscopic cholecystectomy.<sup>125</sup>

### **Antimicrobial Activity**

Turmeric has been shown to inhibit the growth of numerous microorganisms including bacteria, viruses and fungi. An *in vitro* study using a methanol extract of the dried powdered turmeric rhizome inhibited the growth of *Helicobacter pylori*, a Group 1 carcinogen associated with the development of gastric and colon cancer.<sup>126</sup> An aqueous solution of turmeric extract was shown to preserve and extend the shelf life of vacuum-packaged rainbow trout by retarding microbial growth.<sup>127</sup> Histamine producing bacteria (*Vibrio parahaemolyticus*, *Bacillus cereus* and *Proteus mirabilis*) were inhibited by turmeric at 5% concentration. Another study reported the bactericidal activities of turmeric tuber extract and powder against *Escherichia coli* BL-21 strain.<sup>128</sup>

A recent *in vitro* study showed that an aqueous extract of turmeric repressed hepatitis B virus replication through enhancing the level of p53 protein. The authors concluded that turmeric can be used as a safe and specific drug for patients with liver diseases caused by HBV infection. In addition, turmeric did not have any cytotoxic effects on liver cells.<sup>129</sup>

A crude ethanolic extract of turmeric exhibited an inhibition zone range of 6.1 to 26.0mm when tested for antifungal activity by agar disc diffusion method against 29 clinical strains of dermatophytes.<sup>130</sup> The ethanolic extract of turmeric also exhibited excellent (100%) phytotoxic activity against *Lemna minor*. It was also found to possess good antifungal activities against *Trichophyton longifusus* (65%).<sup>131</sup>

### **Diabetes Activity**

Turmeric has shown potential against diabetes in numerous animal models and *in vitro* studies. In the case of diabetes mellitus there is an increase in blood glucose due to low or null production and release of insulin, which produces a deterioration in all the cells of the body. Turmeric does not modify insulin levels and glucose levels but, through well-demonstrated mechanisms, it reduces inflammatory processes and oxidative stress, which are present in diabetic patients and are a consequence of the high blood glucose levels. In this sense it is known that chronic high levels of glucose in blood can lead to alterations at the vascular level, which leads to processes of local ischemia and a production of free radicals and inflammation. Turmeric reduces the complication due to the chronic high level of glycemia in diabetic patients by reducing oxidative stress and/or inflammation and apoptosis in certain tissues of the human body, such as the brain. As a consequence, turmeric may be used in the treatment of diabetes mellitus complications.<sup>132</sup>

Preliminary results of a 2015 study investigating the effect of turmeric as an adjuvant to antidiabetic therapy show that turmeric powder improved some lipid parameters and decreased an anti-inflammatory marker in type 2 diabetics. In India 60 patients who had been type 2 diabetics for less than two years and currently taking metformin were randomised into two groups: group I received metformin; group II received turmeric capsules in addition to metformin for four weeks. Gelatine containing capsules were prepared from dried, powdered turmeric. The daily dose consisted of 2g of turmeric powder providing 46mg of curcumin. Turmeric capsules were ingested two hours after taking metformin. The improvement was statistically significant. Fasting plasma glucose fell significantly in both groups, although to a greater extent in those receiving turmeric. Turmeric lowered LDL-cholesterol (by 9.0%), non HDL-cholesterol (by 6.9%) and LDL/HDL ratio (by 16.6%). As expected, turmeric reduced plasma levels of MDA (malonaldehyde, a measure of lipid peroxidation). There were no significant changes in fasting plasma insulin, insulin resistance, glucose/insulin ratio or other lipids. Turmeric markedly reduced serum levels of the inflammatory marker, high-sensitivity C-reactive protein.<sup>133</sup>

Turmeric rhizome extracts showed high potential to inhibit glucosidase activities and glycation reactions in a 2014 study. The extracts were also effective in scavenging free radicals and inhibiting low-density lipoprotein and cellular oxidations and angiotensin converting enzyme activity. The high antidiabetic, dietary antioxidants and antihypertensive capacities of turmeric rhizome revealed in this research highlighted its potential to serve as a source for preventive and therapeutic agents for the management of diabetes and related disorders.<sup>134</sup>

End-stage renal disease (ESRD) due to type 2 diabetic nephropathy is a very common condition which is increasing in prevalence, and is associated with high global levels of mortality and morbidity. Both proteinuria and transforming growth factor- $\beta$  (TGF- $\beta$ ) may contribute to the development of ESRD in patients with diabetic nephropathy. Experimental studies indicate that turmeric improves diabetic nephropathy by suppressing TGF- $\beta$ . A randomised, double-blind and placebo-controlled study in Iran investigated the effects of turmeric on serum and urinary TGF- $\beta$ , interleukin-8 (IL-8) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), as well as proteinuria, in patients with overt type 2 diabetic nephropathy. The study consisted of 40 patients with overt type 2 diabetic nephropathy that were randomly assigned to either the trial group (n = 20) and a control group (n = 20). Each patient in the trial group received one capsule with each meal containing 500mg turmeric, of which 22.1mg was the active ingredient curcumin (three capsules daily) for two months. The control group received three capsules identical in colour and size containing starch for the same 2 months. Serum levels of TGF- $\beta$  and IL-8 and urinary protein excretion and IL-8 decreased significantly comparing the pre- and post-turmeric supplementation values. The authors of this study concluded that short-term turmeric supplementation can attenuate proteinuria, TGF- $\beta$  and IL-8 in patients with overt type 2 diabetic nephropathy and can be administered as a safe adjuvant therapy for these patients.<sup>135</sup>

A Swedish study examined the effects of turmeric on postprandial plasma glucose, insulin levels and glycemic index in healthy subjects. Fourteen healthy subjects were assessed in a crossover trial. A standard 75g oral glucose tolerance test (OGTT) was administered together with capsules containing a placebo or turmeric. The study found that the

ingestion of 6g of turmeric increased postprandial serum insulin levels but had no effect on plasma glucose levels or glycemic index in these healthy subjects. The results indicate that turmeric may have an effect on insulin secretion.<sup>136</sup>

A study using mice has shown that turmeric is a promising ingredient of functional food for the prevention and/or amelioration of type 2 diabetes and that curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone mainly contribute to the effects via peroxisome proliferator-activated receptor (PPAR)- $\gamma$  activation. Turmeric extract significantly suppressed an increase in blood glucose level in type 2 diabetic mice.<sup>137</sup>

Another study aimed at comparing the modulatory effects of turmeric against diabetes and oxidative stress induced by streptozotocin and nicotinamide in rats. The results proved that turmeric significantly alleviates signs of diabetes (hyperglycaemia and dyslipidaemia) and elevations in atherogenic indices and cellular toxicity in the rats by increasing the production of insulin, enhancing the antioxidant defence system and decreasing lipid peroxidation.<sup>138</sup> Another rat study indicated that turmeric is effective against the development of diabetic cataract.<sup>139</sup>

A study dealing with the effects of freeze dried rhizome powder of turmeric dissolved in milk on normal as well as diabetic rat models. Diabetes of type II and type I was within three days of a single administration of doses of 45 and 65mg kg<sup>-1</sup> of streptozotocin respectively. Various parameters such as blood glucose levels, triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), very low density lipoprotein (VLDL), low density lipoprotein (LDL), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), alkaline phosphatase (ALP), creatinine, haemoglobin (Hb), urine protein and urine sugar in addition to body weight (bw) were taken into consideration and were analysed after administration of variable doses of rhizome powder. The dose of 200mg kg<sup>-1</sup> was identified as the most effective dose as it increased HDL, Hb and bw ( $p < 0.05$ ) with significant decrease in the levels of blood glucose, lipid profile and hepatoprotective enzymes ( $p < .001$ ).<sup>140</sup>

An aqueous extract of turmeric was shown to have insulin releasing action in an *in vitro* study investigating its effect on tissues involved in glucose

homeostasis. The extract was prepared by soaking 100g of ground turmeric in 1L of water, which was filtered and stored at -20°C prior to use.<sup>141</sup>

An aqueous extract of turmeric has been shown to inhibit human pancreatic amylase activity in an *in vitro* study. This action thereby reduces the rate of starch hydrolysis leading to lowered glucose levels.<sup>142</sup>

Turmeric extract was shown to have a strong recovery effect (greater than 20%) on cisplatin-induced nephrotoxicity in an *in vitro* test. It was suggested that additional studies should be conducted to determine if turmeric possesses novel therapeutic agents that can be used for the prevention or treatment of renal disorders.<sup>143</sup>

### Antidepressant Activity

A recent animal study suggests that turmeric has antidepressant properties and may be a useful agent against depression. The study was undertaken to determine the behavioural, neurochemical and neuroendocrine effects of the ethanolic extract of turmeric using the forced swimming test (FST) in mice. The results suggested that antidepressant properties of the ethanolic extract of turmeric were mediated through regulations of neurochemical and neuroendocrine systems.<sup>144</sup>

An earlier study demonstrated that aqueous extracts of turmeric had specifically antidepressant effects *in vivo*. The results showed that activity of turmeric in depression may be mediated in part through monoamine oxidase A inhibition in mouse brains.<sup>145</sup>

### Protection Against Chemical Insults

Several animal studies have shown that turmeric can protect the normal cells, tissues and organs against the damage caused by external insults including reducing arsenic and fluoride toxicity, and carbon tetrachloride induced hepatotoxicity.<sup>146,147,148</sup>

A 2017 study reported the antioxidant properties and the protective effects of turmeric against induced toxicity *in vivo*. The study found that turmeric supplementation could protect against pesticide-induced hematological perturbations and hepatic injuries in rats, plausibly by the up-regulation of antioxidant enzymes and inhibition of lipid peroxidation to confer the protective effect.<sup>149</sup>

### Larvicidal and Insecticidal Activity

In a 2017 *in vitro* study it was discovered that turmeric and ginger extracts have high scolicidal (agents used for hydatid cysts which are the larval cyst of a tapeworm) activity and could be used as effective scolicidal agents against *Echinococcus protoscoleces*. Hydatid disease is an important economic and human public health problem with a wide geographical distribution. Surgical excision remains the primary treatment and the only hope for complete cure of hydatosis. The most important complications arising from surgical excision, however, is recurrence, which is due to dissemination of protoscolices during the surgery. Presurgical inactivation of the contents of the hydatid cyst by injection of scolicidal agent into the cyst has been used as adjunct to surgery in order to overcome the risk of recurrence. In this study ethanolic extracts of turmeric and ginger were tested as scolicidal agent for *Echinococcus protoscoleces*.<sup>150</sup>

In 2016 a Malaysian study revealed that turmeric exhibits good anthelmintic properties. This study evaluated the *in vitro* effects of ethanolic extract of turmeric as a biological nematicide against third stage Haemonchus larvae isolated from sheep. Turmeric showed anthelmintic activity in a dose-dependent manner with 78% worm mortality within 24 hours of exposure at the highest dose rate of 200mg/mL.<sup>151</sup>

The results of a 2012 study show that turmeric may serve as a natural larvicidal agent. A hydrodistillate extract of turmeric demonstrated larvicidal activity against the dengue vector *Aedes aegypti*, the yellow fever mosquito. Early instar larvae were more susceptible to the extract than the late instar larvae and pupae.<sup>152</sup>

The essential oil of turmeric was found to be insecticidal in an Indian study. The study investigated the contact and fumigant toxicity of turmeric and its effect on progeny production in three stored-product beetles, *Rhyzopertha dominica* F. (lesser grain borer), *Sitophilus oryzae* L. (rice weevil), and *Tribolium castaneum* Herbst (red flour beetle). The oil was insecticidal in both contact and fumigant toxicity assays.<sup>153</sup>

### Antiobesity Activity

Turmeric may contribute to the decreasing of body fat and regulating leptin secretion a 2016 *in vivo* study found. Leptin is a peptide hormone produced by adipocytes and its concentration is increased in proportion to the amount of the adipocytes. The study examined the effects of turmeric on the regulation of adiposity and leptin levels in adipocytes and rats fed a high-fat and high-cholesterol diet.<sup>154</sup>

### Indications

- Adjunctive cancer treatment, chemoprevention (to reverse, suppress or prevent the development of cancer), chemosensitisation (makes tumour cells more sensitive to chemotherapy)
- Inflammatory conditions such as generalised chronic inflammation, arthritis, osteoarthritis, irritable bowel syndrome (IBS), inflammatory bowel disease, asthma, eczema, psoriasis, lupus nephritis
- Cardiovascular disease prophylaxis, adjunct in the treatment of hyperlipidaemia
- Dyspepsia, peptic ulcer
- Infections such as the common cold
- Adjunctive diabetes treatment
- Liver and gallbladder dysfunction such as hangover, jaundice and hepatitis
- Menstrual disorders
- Depression, Alzheimer's disease (still being investigated)
- Topically for skin conditions and cancer associated lesions, sprains and strains, adjunct in periodontitis and gingivitis

### Energetics

Warming, drying.

### Use in Pregnancy

When used as a spice turmeric is most likely to be safe however the safety of therapeutic doses has not been established. In traditional Ayurvedic and Chinese medicine taking turmeric in the last two weeks of pregnancy is said to simplify the birth,

increase the health of the mother and child and decrease the pain of the birth.<sup>155,156</sup>

### Drug Interactions

Caution with dexamethasone (an anti-inflammatory medication), sulphasalazine (a disease-modifying antirheumatic drug), tacrolimus (an immunosuppressive drug), talinolol (a beta blocker), anticoagulant/antiplatelet and antidiabetic drugs. Combination may be beneficial with high alcohol ingestion and non-steroidal anti-inflammatory drugs (NSAIDs).

### Contraindications

Contraindicated in patients with obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary disease. High doses are probably best avoided in males and females wanting to conceive. Contraindicated when used in patients allergic to turmeric, any of its constituents (including curcumin), certain yellow food colourings or other members of the Zingiberaceae (ginger) family.<sup>157</sup>

### Administration and Dosage

Liquid Extract:	1:2
Alcohol:	60%
Weekly Dosage:	35 to 150mL

### Remedy Recipes

#### Wound Paste

To make a paste for wounds: put 30g dried turmeric powder in a pan with 150mL water and simmer to a thick paste. Place gauze on affected area and apply the paste for a few minutes, 3 times a day.

#### Golden Milk

Blend the following ingredients in a high-speed blender until smooth: 1 cup of milk of choice (almond, coconut, cashew, macadamia or dairy), ½ tsp turmeric, 1/4 tsp cinnamon, pinch of black pepper (increases absorption), tiny piece of fresh, peeled ginger root or a pinch of ginger powder, honey to taste. Pour into a small saucepan and heat to just below boiling point. Whizz again in the blender to froth (optional).

## References

- Pharmaceutical Press Editorial. Herbal Medicines. 4th ed. London: Pharmaceutical Press; 2013. p. 716.
- The Plant List. [Internet]. Kew and Missouri: Royal Botanic Gardens, Kew and Missouri Botanical Garden; c2013 Version 1.1 [accessed 2017 August 10] Available from <http://www.theplantlist.org/tp11/record/kew-102273>
- van Wyk B, Wink M. Medicinal Plants of the World. Pretoria: Briza Publications; 2004. p. 118.
- Ross I. Medicinal Plants of the World. Totowa (NJ): Humana Press; 1999. p. 140.
- Food Standards.gov.au. Additives Overview [Internet]. Barton (ACT): Food Standards Australia and New Zealand; c2012 [cited 2013 Jul 15]. Available from: <http://www.foodstandards.gov.au/consumer/additives/additiveoverview/pages/default.aspx>
- Grieve M. A Modern Herbal. Middlesex: Penguin Books; 1973. p. 823.
- Stargrove M, Treasure J, McKee D. Herb, Nutrient and Drug Interactions. St. Louis: Mosby Elsevier; 2008. p. 160
- Castleman M. The New Healing Herbs. Dingley: Hinkler Books; 2001. p. 435.
- Turmeric latte: the 'golden milk' with a cult following. The Guardian [Internet] 2016 May 12. [accessed 2017 August 14] Available at <https://www.theguardian.com/lifeandstyle/2016/may/11/turmeric-latte-golden-milk-cult-following-alternative-coffee>
- Ravindran PK, Nirmal Babu K, Sivaraman K eds. Turmeric: the genus *Curcuma*. Boca Raton (FL): CRC Press; 2007.
- Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. *Adv Exp Med Biol.* 2007;595:1-75.
- Gupta SC, Sung B, Kim JH, Prasad S, Li S, Aggarwal BB. Multitargeting by turmeric, the golden spice: From kitchen to clinic. *Mol Nutr Food Res.* 2012 Aug 13. doi: 10.1002/mnfr.201100741. [Epub ahead of print]
- Castleman M. p. 435.
- Panda AK, Chakraborty D, Sarkar I, Khan T, Sa G. New insights into therapeutic activity and anticancer properties of curcumin. *J Exp Pharmacol.* 2017 Mar 31;9:31-45. doi: 10.2147/JEP.S70568. eCollection 2017.
- Majeed M, Badmaev V. Curcuminoids – antioxidant phytonutrients. Piscataway (NJ): Nutriscience Publishers; 2003. p. 1.
- Aggarwal BB. Curcumin: the Indian solid gold.
- Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic.
- Hempfen C, Fischer T. A Materia Medica for Chinese Medicine. 2nd ed. Munich: Churchill Livingstone Elsevier; 2007. p. 536.
- de Jager P. Turmeric: The Ayurvedic Spice of Life [Internet]. Boulder (CO): OM Organics; c2003 [cited 2013 Jul 17]. Available from: <http://www.bioponic.com/pdfs/TurmericAyurveda.pdf>
- Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic.
- Castleman M. p. 435-436.
- Stargrove M. p. 161.
- Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic.
- European Scientific Co-operative on Phytotherapy. p. 107.
- Li S, Yuan W, Deng G, Wang P, Yang P, Aggarwal B. Chemical composition and product quality control of turmeric (*Curcuma longa* L). *Pharm Crops.* 2011;2:28-54.
- van Wyk p. 118.
- European Scientific Co-operative on Phytotherapy. ESCOP monographs. 2nd ed. Exeter: Thieme; 2003. p. 107.
- Pharmaceutical Press Editorial. p. 716
- PubMed.gov [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine; c2009 [cited 2013 Jul 8]. Available from <http://www.ncbi.nlm.nih.gov/pubmed/?term=turmeric>
- Pharmaceutical Press Editorial. p. 717.
- Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol.* 2006 May 14;71(10):1397-421. Epub 2006 Feb 23.
- Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic.
- Pakfetrat M, Basiri F, Malekmakan L, Roozbeh J. Effects of turmeric on uremic pruritus in end stage renal disease patients: a double-blind randomized clinical trial. *J Nephrol.* 2014 Apr;27(2):203-7. doi: 10.1007/s40620-014-0039-2. Epub 2014 Jan 31.
- Clinicaltrials.gov [Internet]. Maryland: US National Institutes of Health; c2012 [cited 2013 Jul 24] Available from <http://www.clinicaltrials.gov/ct2/results?term=turmeric&Search=Search>
- Ammon HP, Wahl MA. Pharmacology of *Curcuma longa*. *Planta Med.* 1991 Feb;57(1):1-7.
- Stargrove M. p. 161.
- Bone K, Mills S. Principles and Practice of Phytotherapy. 2nd ed. Chatswood: Churchill Livingstone Elsevier; 2013. p. 901-2.
- Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The Essential Medicinal Chemistry of Curcumin. *J Med Chem.* 2017 Mar 9;60(5):1620-1637. doi: 10.1021/acs.jmedchem.6b00975. Epub 2017 Jan 11.
- Aggarwal BB, Yuan W, Li S, Gupta SC. Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. *Mol Nutr Food Res.* 2013 Jul 12. doi: 10.1002/mnfr.201200838. [Epub ahead of print]
- The Herbal Extract Company of Australia manufacturing brochure. Concentration ratio: Full spectrum 1:1 liquid herbal extracts.
- Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The Essential Medicinal Chemistry of Curcumin. *J Med Chem.* 2017 Mar 9;60(5):1620-1637. doi: 10.1021/acs.jmedchem.6b00975. Epub 2017 Jan 11.
- Gupta SC, Kismali G, Aggarwal BB. Curcumin, a component of turmeric: from farm to pharmacy. *Biofactors.* 2013 Jan-Feb;39(1):2-13. doi: 10.1002/biof.1079. Epub 2013 Jan 22.
- Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. *Ann N Y Acad Sci.* 2005 Nov;1056:206-17.
- Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J.* 2013 Jan;15(1):195-218. doi: 10.1208/s12248-012-9432-8. Epub 2012 Nov 10.
- Aggarwal BB. Nuclear factor-kappaB: the enemy within. *Cancer Cell.* 2004 Sep;6(3):203-8.
- Shakeri F, Soukhtanloo M, Boskabady MH. The effect of hydro-ethanolic extract of *Curcuma longa* rhizome and curcumin on total and differential WBC and serum oxidant, antioxidant biomarkers in rat model of asthma. *Iran J Basic Med Sci.* 2017 Feb;20(2):155-165. doi: 10.22038/ijbms.2017.8241.
- Daily JW, Yang M, Park S. Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *J Med Food.* 2016 Aug;19(8):717-29. doi: 10.1089/jmf.2016.3705.
- Srivastava S, Saksena AK, Khattri S, Kumar S, Dagur RS. Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology.* 2016 Dec;24(6):377-388. Epub 2016 Oct 19.

49. Madhu K, Chanda K, Saji MJ. Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. *Inflammopharmacology*. 2013 Apr;21(2):129-36. doi: 10.1007/s10787-012-0163-3. Epub 2012 Dec 16.
50. Bowden RG, Moreillon J, Deike E, Griggs J, Wilson R, Shelmadine B, et al. The use of an anti-inflammatory supplement in patients with chronic kidney disease. *J Complement Integr Med*. 2013 Jul 1;10(1):1-10. doi: 10.1515/jcim-2012-0011.
51. Khajehdehi P, Zanjanejad B, Aflaki E, Nazarinia M, Azad F, Malekmakan L, et al. J Ren Nutr. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. *2012 Jan;22(1):50-7*. doi: 10.1053/j.jrn.2011.03.002. Epub 2011 Jul 13.
52. Stoyell KA, Mappus JL, Gandhi MA. Clinical efficacy of turmeric use in gingivitis: A comprehensive review. *Complement Ther Clin Pract*. 2016 Nov;25:13-17. doi: 10.1016/j.ctcp.2016.08.004. Epub 2016 Aug 2.
53. Kandwal A, Mamgain RK, Mamgain P. Comparative evaluation of turmeric gel with 2% chlorhexidine gluconate gel for treatment of plaque induced gingivitis: A randomized controlled clinical trial. *Ayu*. 2015 Apr-Jun;36(2):145-50. doi: 10.4103/0974-8520.175537.
54. Behal R, Mali AM, Gilda SS, Paradkar AR. Evaluation of local drug-delivery system containing 2% whole turmeric gel used as an adjunct to scaling and root planing in chronic periodontitis: A clinical and microbiological study. *J Indian Soc Periodontol*. 2011 Jan;15(1):35-8. doi: 10.4103/0972-124X.82264.
55. Shakeri F, Soukhtanloo M, Boskabady MH. The effect of hydro-ethanolic extract of Curcuma longa rhizome and curcumin on total and differential WBC and serum oxidant, antioxidant biomarkers in rat model of asthma. *Iran J Basic Med Sci*. 2017 Feb;20(2):155-165. doi: 10.22038/ijbms.2017.8241.
56. Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic.
57. Chandrasekaran CV, Sundarajan K, Edwin JR, Gururaja GM, Mundkinajeddu D, Agarwal A. Immune-stimulatory and anti-inflammatory activities of Curcuma longa extract and its polysaccharide fraction. *Pharmacognosy Res*. 2013 Apr;5(2):71-9. doi: 10.4103/0974-8490.110527.
58. Taty Anna K, Elvy Suhana MR, Das S, Faizah O, Hamzaini AH. Anti-inflammatory effect of Curcuma longa (turmeric) on collagen-induced arthritis: an anatomico-radiological study. *Clin Ter*. 2011;162(3):201-7.
59. Funk JL, Frye JB, Oyarzo JN, Kuscuoglu N, Wilson J, McCaffrey G, et al. Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis. *Arthritis Rheum*. 2006 Nov;54(11):3452-64.
60. Boonjaraspinyo S, Boonmars T, Aromdee C, Srisawangwong T, Kaewsamut B, Pinlaor S, et al. Turmeric reduces inflammatory cells in hamster opisthorchiasis. *Parasitol Res*. 2009 Oct;105(5):1459-63. doi: 10.1007/s00436-009-1553-3. Epub 2009 Jul 25.
61. Seo SW, Bae GS, Kim SG, Yun SW, Kim MS, Yun KJ, et al. Protective effects of Curcuma longa against cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. *Int J Mol Med*. 2011 Jan;27(1):53-61. doi: 10.3892/ijmm.2010.548. Epub 2010 Nov 8.
62. Lantz RC, Chen GJ, Solyom AM, Jolad SD, Timmermann BN. The effect of turmeric extracts on inflammatory mediator production. *Phytomedicine*. 2005 Jun;12(6-7):445-52.
63. Kumar GS, Nayaka H, Dharmesh SM, Salimath PV. Free and bound phenolic antioxidants in amla (*Embllica officinalis*) and turmeric (*Curcuma longa*). *Journal of Food Composition and Analysis*. 2006 Aug;19(5):446-52.
64. Shalini VK, Srinivas L. Lipid peroxide induced DNA damage: protection by turmeric (*Curcuma longa*). *Mol Cell Biochem*. 1987 Sep;77(1):3-10.
65. Coghly HH, Taylor A, Angel MF, Salahudeen AK. Effect of turmeric, turmerin and curcumin on H2O2-induced renal epithelial (LLC-PK1) cell injury. *Free Radic Biol Med*. 1998 Jan 1;24(1):49-54.
66. Betancor-Fernández A, Pérez-Gálvez A, Sies H, Stahl W. Screening pharmaceutical preparations containing extracts of turmeric rhizome, artichoke leaf, devil's claw root and garlic or salmon oil for antioxidant capacity. *J Pharm Pharmacol*. 2003 Jul;55(7):981-6.
67. Jin S, Hong JH, Jung SH, Cho KH. Turmeric and laurel aqueous extracts exhibit in vitro anti-atherosclerotic activity and in vivo hypolipidemic effects in a zebrafish model. *J Med Food*. 2011 Mar;14(3):247-56. doi: 10.1089/jmf.2009.1389.
68. Samanta L, Panigrahi J, Bhanja S, Chainy GB. Effect of turmeric and its active principle curcumin on t(3)-induced oxidative stress and hyperplasia in rat kidney: a comparison. *Indian J Clin Biochem*. 2010 Oct;25(4):393-7. doi: 10.1007/s12291-010-0046-6. Epub 2010 Oct 8.
69. Unlu A, Nayir E, Dogukan Kalenderoglu M, Kirca O, Ozdogan M. Curcumin (Turmeric) and cancer. *J BUON*. 2016 Sept-Oct;21(5):1050-1060.
70. Hasima N, Aggarwal BB. Cancer-linked targets modulated by curcumin. *Int J Biochem Mol Biol*. 2012;3(4):328-51. Epub 2012 Dec 24.
71. Dimas K, Tsimplouli C, Houchen C, Pantazis P, Sakellariadis N, Tsangaris GT, et al. An Ethanol Extract of Hawaiian Turmeric: Extensive In Vitro Anticancer Activity Against Human Colon Cancer Cells. *Altern Ther Health Med*. 2015;21 Suppl 2:46-54.
72. Ghalaut VS, Sangwan L, Dahiya K, Ghalaut PS, Dhankhar R, Saharan R. Effect of imatinib therapy with and without turmeric powder on nitric oxide levels in chronic myeloid leukemia. *J Oncol Pharm Pract*. 2012 Jun;18(2):186-90. doi: 10.1177/1078155211416530. Epub 2011 Aug 15.
73. Kim JH, Gupta SC, Park B, Yadav VR, Aggarwal BB. Turmeric (*Curcuma longa*) inhibits inflammatory nuclear factor (NF)- $\kappa$ B and NF- $\kappa$ B-regulated gene products and induces death receptors leading to suppressed proliferation, induced chemosensitization, and suppressed osteoclastogenesis. *Mol Nutr Food Res*. 2012 Mar;56(3):454-65. doi: 10.1002/mnfr.201100270. Epub 2011 Dec 7.
74. Kuttan R, Sudheeran PC, Josph CD. Turmeric and curcumin as topical agents in cancer therapy. *Tumori*. 1987 Feb 28;73(1):29-31.
75. Hastak K, Lubri N, Jakhi SD, More C, John A, Ghaisas SD, et al. Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis. *Cancer Lett*. 1997 Jun 24;116(2):265-9.
76. Ramachandran C, Resek AP, Escalon E, Aviram A, Melnick SJ. Potentiation of gemcitabine by Turmeric Force in pancreatic cancer cell lines. *Oncol Rep*. 2010 Jun;23(6):1529-35.
77. Thapliyal R, Naresh KN, Rao KV, Maru GB. Inhibition of nitrosodiethylamine-induced hepatocarcinogenesis by dietary turmeric in rats. *Toxicol Lett*. 2003 Mar 20;139(1):45-54.
78. El-Shahat M, El-Abd S, Alkafafy M, El-Khatib G. Potential chemoprevention of diethylnitrosamine-induced hepatocarcinogenesis in rats: myrrh (*Commiphora molmol*) vs. turmeric (*Curcuma longa*). *Acta Histochem*. 2012 Sep;114(5):421-8. doi: 10.1016/j.acthis.2011.08.002. Epub 2011 Aug 26.
79. Garg R, Ingle A, Maru G. Dietary turmeric modulates DMBA-induced p21ras, MAP kinases and AP-1/NF-kappaB pathway to alter cellular responses during hamster buccal pouch carcinogenesis. *Toxicol Appl Pharmacol*. 2008 Nov 1;232(3):428-39. doi: 10.1016/j.taap.2008.07.007. Epub 2008 Jul 19.
80. Nishimura Y, Kitagishi Y, Yoshida H, Okumura N, Matsuda S. Ethanol extracts of black pepper or turmeric down-regulated SIRT1 protein expression in Daudi culture cells. *Mol Med Rep*. 2011 Jul-Aug;4(4):727-30. doi: 10.3892/mmr.2011.487. Epub 2011 May 13.

81. Omoregie SN, Omoruyi FO, Wright VF, Jones L, Zimba PV. J Med Food.. Antiproliferative Activitis of Lesser Galangal (*Alpinia officinarum* Hance Jam1), Turmeric (*Curcuma longa* L.), and Ginger (*Zingiber officinale* Rosc.) Against Acute Monocytic Leukemia. 2013 Jul 2 [Epub ahead of print].
82. Kuttan R, Bhanumathy P, Nirmala K, George MC. Potential anticancer activity of turmeric (*Curcuma longa*). *Cancer Lett*. 1985 Nov;29(2):197-202.
83. Kim J, Ha HL, Moon HB, Lee YW, Cho CK, Yoo HS, et al. Chemopreventive effect of *Curcuma longa* Linn on liver pathology in HBx transgenic mice. *Integr Cancer Ther*. 2011 Jun;10(2):168-77. doi: 10.1177/1534735410380613. Epub 2010 Dec 29.
84. Deshpande SS, Ingle AD, Maru GB. Chemopreventive efficacy of curcumin-free aqueous turmeric extract in 7,12-dimethylbenz[a]anthracene-induced rat mammary tumorigenesis. *Cancer Lett*. 1998 Jan 16;123(1):35-40.
85. El-Shahat M, El-Abd S, Alkafafy M, El-Khatib G. *Acta Histochem*. Potential chemoprevention of diethylnitrosamine-induced hepatocarcinogenesis in rats: myrrh (*Commiphora molmol*) vs. turmeric (*Curcuma longa*). 2012 Sep;114(5):421-8. doi: 10.1016/j.acthis.2011.08.002. Epub 2011 Aug 26.
86. Kapadia GJ, Azuine MA, Tokuda H, Hang E, Mukainaka T, Nishino H, et al. Inhibitory effect of herbal remedies on 12-O-tetradecanoylphorbol-13-acetate-promoted Epstein-Barr virus early antigen activation. *Pharmacol Res*. 2002 Mar;45(3):213-20.
87. Polasa K, Raghuram TC, Krishna TP, Krishnaswamy K. Effect of turmeric on urinary mutagens in smokers. *Mutagenesis*. 1992 Mar;7(2):107-9.
88. Deshpande SS, Ingle AD, Maru GB. Inhibitory effects of curcumin-free aqueous turmeric extract on benzo[a]pyrene-induced forestomach papillomas in mice. *Cancer Lett*. 1997 Sep 16;118(1):79-85.
89. Azuine MA, Kayal JJ, Bhide SV. Protective role of aqueous turmeric extract against mutagenicity of direct-acting carcinogens as well as benzo [alpha] pyrene-induced genotoxicity and carcinogenicity. *J Cancer Res Clin Oncol*. 1992;118(6):447-52.
90. Puangsombat K, Jirapakkul W, Smith JS. Inhibitory activity of Asian spices on heterocyclic amines formation in cooked beef patties. *J Food Sci*. 2011 Oct;76(8):T174-80. doi: 10.1111/j.1750-3841.2011.02338.x. Epub 2011 Sep 13.
91. Yue GG, Chan BC, Hon PM, Kennelly EJ, Yeung SK, Cassileth BR, et al. Immunostimulatory activities of polysaccharide extract isolated from *Curcuma longa*. *Int J Biol Macromol*. 2010 Oct 1;47(3):342-7. doi: 10.1016/j.ijbiomac.2010.05.019. Epub 2010 Jun 1.
92. Sharma A, Gautam S, Jadhav SS. Spice extracts as dose-modifying factors in radiation inactivation of bacteria. *J Agric Food Chem*. 2000 Apr;48(4):1340-4.
93. Pal A, Pal AK. Radioprotection of turmeric extracts in bacterial system. *Acta Biol Hung*. 2005;56(3-4):333-43.
94. Flores G. *Curcuma longa* L. extract improves the cortical neural connectivity during the aging process. *Neural Regen Res*. 2017 Jun;12(6):875-880. doi: 10.4103/1673-5374.208542.
95. Flores G. *Curcuma longa* L. extract improves the cortical neural connectivity during the aging process. *Neural Regen Res*. 2017 Jun;12(6):875-880. doi: 10.4103/1673-5374.208542.
96. Vidal B, Vázquez-Roque RA, Gnecco D, Enríquez RG, Floran B, Díaz A, et al. *Curcuma* treatment prevents cognitive deficit and alteration of neuronal morphology in the limbic system of aging rats. *Synapse*. 2017 Mar;71(3). doi: 10.97.1002/syn.21952. Epub 2017 Jan 12.
97. Ma XW, Guo RY. Dose-dependent effect of *Curcuma longa* for the treatment of Parkinson's disease. *Exp Ther Med*. 2017 May;13(5):1799-1805. doi: 10.3892/etm.2017.4225. Epub 2017 Mar 10.
98. Mythri RB, Veena J, Harish G, Shankaranarayana Rao BS, Srinivas Bharath MM. Chronic dietary supplementation with turmeric protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-mediated neurotoxicity in vivo: implications for Parkinson's disease. *Br J Nutr*. 2011 Jul;106(1):63-72. doi: 10.1017/S0007114510005817. Epub 2011 Apr 8.
99. Yuliani S, Widyarini S, Mustofa, Partadiredja G. Turmeric extract inhibits apoptosis of hippocampal neurons of trimethyltin-exposed rats. *Bratisl Lek Listy*. 2017;118(3):142-148. doi: 10.4149/BLL\_2017\_028.
100. Ahmed T, Gilani AH. *Phytother Res*. Therapeutic Potential of Turmeric in Alzheimer's Disease: Curcumin or Curcuminoids? 2013 Jul 19. doi: 10.1002/ptr.5030. [Epub ahead of print]
101. Shytle RD, Tan J, Bickford PC, Rezaei-Zadeh K, Hou L, Zeng J, et al. Optimized turmeric extract reduces  $\beta$ -Amyloid and phosphorylated Tau protein burden in Alzheimer's transgenic mice. *Curr Alzheimer Res*. 2012 May;9(4):500-6.
102. Pyrzanowska J, Piechal A, Blecharz-Klin K, Lehner M, Skórzewska A, Turzyńska D, et al. The influence of the long-term administration of *Curcuma longa* extract on learning and spatial memory as well as the concentration of brain neurotransmitters and level of plasma corticosterone in aged rats. *Pharmacol Biochem Behav*. 2010 May;95(3):351-8. doi: 10.1016/j.pbb.2010.02.013. Epub 2010 Feb 26
103. Thavorn K, Mamdani MM, Straus SE. Efficacy of turmeric in the treatment of digestive disorders: a systematic review and meta-analysis protocol. *Syst Rev*. 2014 Jun 28;3:71. doi: 10.1186/2046-4053-3-71.
104. Deshpande UR, Gadre SG, Raste AS, Pillai D, Bhide SV, Samuel AM. Protective effect of turmeric (*Curcuma longa* L.) extract on carbon tetrachloride-induced liver damage in rats. *Indian J Exp Biol* 1998 Jun;36(6):573-577.
105. Adaramoye OA, Odunewu AO, Farombi EO. Hepatoprotective effect of *Curcuma longa* L. in D-galactosamine induced liver injury in mice: evidence of antioxidant activity. *Afr J Med Med Sci* 2010 Dec;39 Suppl:27-34.
106. Miyakoshi M, Yamaguchi Y, Takagaki R, Mizutani K, Kambara T, Ikeda T, et al. Hepatoprotective effect of sesquiterpenes in turmeric. *Biofactors* 2004;21(1-4):167-70
107. El-Shahat M, El-Abd S, Alkafafy M, El-Khatib G. Potential chemoprevention of diethylnitrosamine-induced hepatocarcinogenesis in rats: Myrrh (*Commiphora molmol*) vs. turmeric (*Curcuma longa*). *Acta Histochem* 2012;114(5):421-28.
108. Kim SW, Ha KC, Choi EK, Jung SY, Kim MG, Kwon DY, et al. The effectiveness of fermented turmeric powder in subjects with elevated alanine transaminase levels: a randomised controlled study. *BMC Complement Altern Med*. 2013 Mar 8;13:58. doi: 10.1186/1472-6882-13-58.
109. Uchio R, Higashi Y, Kohama Y, Kawasaki K, Hirao T, Muroyama K, et al. A hot water extract of turmeric (*Curcuma longa*) suppresses acute ethanol-induced liver injury in mice by inhibiting hepatic oxidative stress and inflammatory cytokine production. *J Nutr Sci*. 2017 Jan 12;6:e3. doi: 10.1017/jns.2016.43. eCollection 2017.
110. Prucksunand C, Indrasukhsri B, Leethochawalit M, Hungspreugs K. Phase II clinical trial on effect of the long turmeric (*Curcuma longa* Linn) on healing of peptic ulcer. *Southeast Asian J Trop Med Public Health*. 2001 Mar;32(1):208-15.
111. Kim DC, Kim SH, Choi BH, Baek NI, Kim D, Kim MJ, et al. *Curcuma longa* extract protects against gastric ulcers by blocking H2 histamine receptors. *Biol Pharm Bull*. 2005 Dec;28(12):2220-4.
112. Bundy R, Walker AF, Middleton RW, Booth J. Turmeric extract may improve irritable bowel syndrome symptomatology in otherwise healthy adults: a pilot study. *J Altern Complement Med*. 2004 Dec;10(6):1015-8.
113. Shimouchi A, Nose K, Takaoka M, Hayashi H, Kondo T. Effect of dietary turmeric on breath hydrogen. *Dig Dis Sci*. 2009 Aug;54(8):1725-9. doi: 10.1007/s10620-008-0550-1. Epub 2008 Nov 26.

114. Bastaki SM, Al Ahmed MM, Al Zaabi A, Amir N, Adeghate E. Effect of turmeric on colon histology, body weight, ulcer, IL-23, MPO and glutathione in acetic-acid-induced inflammatory bowel disease in rats. *BMC Complement Altern Med*. 2016 Feb 23;16:72. doi: 10.1186/s12906-016-1057-5.
115. Thamilikitul V, Bunyapraphatsara N, Dechatiwongse T, Theerapong S, Chantrakul C, Thanaveerasuwan T, et al. Randomized double blind study of *Curcuma domestica* Val. for dyspepsia. *J Med Assoc Thai*. 1989 Nov;72(11):613-20.
116. Yiu WF, Kwan PL, Wong CY, Kam TS, Chiu SM, Chan SW, et al. Attenuation of fatty liver and prevention of hypercholesterolemia by extract of *Curcuma longa* through regulating the expression of CYP7A1, LDL-receptor, HO-1, and HMG-CoA reductase. *J Food Sci*. 2011 Apr;76(3):H80-9. doi: 10.1111/j.1750-3841.2011.02042.x.
117. Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic. *Mol Nutr Food Res*. 2013 Sep;57(9):1510-28. doi: 10.1002/mnfr.201100741. Epub 2012 Aug 13.
118. Mesa MD, Aguilera CM, Ramírez-Tortosa CL, Ramírez-Tortosa MC, Quiles JL, Baró L, et al. Oral administration of a turmeric extract inhibits erythrocyte and liver microsome membrane oxidation in rabbits fed with an atherogenic diet. *Nutrition*. 2003 Sep;19(9):800-4.
119. Ramírez-Tortosa MC, Mesa MD, Aguilera MC, Quiles JL, Baró L, Ramirez-Tortosa CL, et al. Oral administration of a turmeric extract inhibits LDL oxidation and has atherocholesterolemic effects in rabbits with experimental atherosclerosis. *Atherosclerosis*. 1999 Dec;147(2):371-8.
120. Vaughn AR, Branum A, Sivamani RK. Effects of Turmeric (*Curcuma longa*) on Skin Health: A Systematic Review of the Clinical Evidence. *Phytother Res*. 2016 Aug;30(8):1243-64. doi: 10.1002/ptr.5640. Epub 2016 May 23.
121. Sarafian G, Afshar M, Mansouri P, Asgarpanah J, Raoufinejad K, Rajabi M. Topical Turmeric Microemulgel in the Management of Plaque Psoriasis; A Clinical Evaluation. *Iranian Journal of Pharmaceutical Research: IJPR*. 2015;14(3):865-876.
122. Saelee C, Thongrakard V, Tencomnao T. Effects of Thai medicinal herb extracts with anti-psoriatic activity on the expression on NF- $\kappa$ B signaling biomarkers in HaCaT keratinocytes. *Molecules*. 2011 May 10;16(5):3908-32. doi: 10.3390/molecules16053908.
123. Kundu S, Biswas TK, Das P, Kumar S, De DK. Turmeric (*Curcuma longa*) rhizome paste and honey show similar wound healing potential: a preclinical study in rabbits. *Int J Low Extrem Wounds*. 2005 Dec;4(4):205-13.
124. Sumiyoshi M, Kimura Y. Effects of a turmeric extract (*Curcuma longa*) on chronic ultraviolet B irradiation-induced skin damage in melanin-possessing hairless mice. *Phytomedicine*. 2009 Dec;16(12):1137-43. doi: 10.1016/j.phymed.2009.06.003. Epub 2009 Jul 4.
125. Agarwal KA, Tripathi CD, Agarwal BB, Saluja S. Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: a double-blind, randomized placebo-controlled study. *Surg Endosc*. 2011 Dec;25(12):3805-10. doi: 10.1007/s00464-011-1793-z. Epub 2011 Jun 14.
126. Mahady GB, Pendland SL, Yun G, Lu ZZ. Turmeric (*Curcuma longa*) and curcumin inhibit the growth of *Helicobacter pylori*, a group 1 carcinogen. *Anticancer Res*. 2002 Nov-Dec;22(6C):4179-81.
127. Pezeshk S, Rezaei M, Hosseini H. Effects of turmeric, shallot extracts, and their combination on quality characteristics of vacuum-packaged rainbow trout stored at 4  $\pm$  1  $^{\circ}$ C. *J Food Sci*. 2011 Aug;76(6):M387-91. doi: 10.1111/j.1750-3841.2011.02242.x. Epub 2011 Jul 5.
128. Sathishkumar M, Sneha K, Yun YS. Immobilization of silver nanoparticles synthesized using *Curcuma longa* tuber powder and extract on cotton cloth for bactericidal activity. *Bioresour Technol*. 2010 Oct;101(20):7958-65. doi: 10.1016/j.biortech.2010.05.051. Epub 2010 Jun 11.
129. Kim HJ, Yoo HS, Kim JC, Park CS, Choi MS, Kim M, et al. Antiviral effect of *Curcuma longa* Linn extract against hepatitis B virus replication. *J Ethnopharmacol*. 2009 Jul 15;124(2):189-96. doi: 10.1016/j.jep.2009.04.046. Epub 2009 May 3.
130. Wuthi-udomlert M, Grisanapan W, Luanratana O, Caichompo W. Antifungal activity of *Curcuma longa* grown in Thailand. *Southeast Asian J Trop Med Public Health*. 2000;31 Suppl 1:178-82.
131. Khattak S, Saeed-ur-Rehman, Ullah Shah H, Ahmad W, Ahmad M. Biological effects of indigenous medicinal plants *Curcuma longa* and *Alpinia galanga*. *Fitoterapia*. 2005 Mar;76(2):254-7.
132. Flores G. *Curcuma longa* L. extract improves the cortical neural connectivity during the aging process. *Neural Regen Res*. 2017 Jun;12(6):875-880. doi: 10.4103/1673-5374.208542.
133. Maithili Karpaga Selvi N, Sridhar MG, Swaminathan RP, Sripradha R. Efficacy of Turmeric as Adjuvant Therapy in Type 2 Diabetic Patients. *Indian J Clin Biochem*. 2015 Apr;30(2):180-6. doi: 10.1007/s12291-014-0436-2. Epub 2014 May 8.
134. Lekshmi PC, Arimboor R, Nisha VM, Menon AN, Raghu KG. In vitro antidiabetic and inhibitory potential of turmeric (*Curcuma longa* L) rhizome against cellular and LDL oxidation and angiotensin converting enzyme. *J Food Sci Technol*. 2014 Dec;51(12):3910-7. doi: 10.1007/s13197-013-0953-7. Epub 2013 Feb 15.
135. Khajehdehi P, Pakfetrat M, Javidnia K, Azad F, Malekmakan L, Nasab MH, et al. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor- $\beta$  and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. *Scand J Urol Nephrol*. 2011 Nov;45(5):365-70. doi: 10.3109/00365599.2011.585622. Epub 2011 May 31.
136. Wickenberg J, Ingemansson SL, Hlebowicz J. Effects of *Curcuma longa* (turmeric) on postprandial plasma glucose and insulin in healthy subjects. *Nutr J*. 2010 Oct 12;9:43. doi: 10.1186/1475-2891-9-43.
137. Kuroda M, Mimaki Y, Nishiyama T, Mae T, Kishida H, Tsukagawa M, et al. Hypoglycemic effects of turmeric (*Curcuma longa* L. rhizomes) on genetically diabetic KK-Ay mice. *Biol Pharm Bull*. 2005 May;28(5):937-9.
138. Madkor HR, Mansour SW, Ramadan G. Modulatory effects of garlic, ginger, turmeric and their mixture on hyperglycaemia, dyslipidaemia and oxidative stress in streptozotocin-nicotinamide diabetic rats. *Br J Nutr*. 2011 Apr;105(8):1210-7. doi: 10.1017/S0007114510004927. Epub 2010 Dec 10.
139. Suryanarayana P, Saraswat M, Mrudula T, Krishna TP, Krishnaswamy K, Reddy GB. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. *Invest Ophthalmol Vis Sci*. 2005 Jun;46(6):2092-9.
140. Rai PK, Jaiswal D, Mehta S, Rai DK, Sharma B, Watal G. Effect of *Curcuma longa* freeze dried rhizome powder with milk in STZ induced diabetic rats. *Indian J Clin Biochem*. 2010 Apr;25(2):175-81. doi: 10.1007/s12291-010-0032-z. Epub 2010 May 27.
141. Mohankumar S, McFarlane JR. An aqueous extract of *Curcuma longa* (turmeric) rhizomes stimulates insulin release and mimics insulin action on tissues involved in glucose homeostasis in vitro. *Phytother Res*. 2011 Mar;25(3):396-401. doi: 10.1002/ptr.3275. Epub 2010 Aug 23.
142. Ponnusamy S, Ravindran R, Zinjarde S, Bhargava S, Ravi Kumar A. Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect in vitro. *Evid Based Complement Alternat Med*. 2011;2011. pii: 515647. doi: 10.1155/2011/515647. Epub 2010 Sep 23.
143. Sohn SH, Lee H, Nam JY, Kim SH, Jung HJ, Kim Y, et al. Screening of herbal medicines for the recovery of cisplatin-induced nephrotoxicity. *Environ Toxicol Pharmacol*. 2009 Sep;28(2):206-12. doi: 10.1016/j.etap.2009.04.005. Epub 2009 Apr 15.

144. Xia X, Cheng G, Pan Y, Xia ZH, Kong LD. Behavioral, neurochemical and neuroendocrine effects of the ethanolic extract from *Curcuma longa* L. in the mouse forced swimming test. *J Ethnopharmacol.* 2007 Mar 21;110(2):356-63. Epub 2006 Oct 17.
145. Yu ZF, Kong LD, Chen Y. Antidepressant activity of aqueous extracts of *Curcuma longa* in mice. *J Ethnopharmacol.* 2002 Nov;83(1-2):161-5.
146. Karim MR, Haque A, Islam K, Ali N, Salam KA, Saud ZA, et al. Protective effects of the dietary supplementation of turmeric (*Curcuma longa* L.) on sodium arsenite-induced biochemical perturbation in mice. *Bangladesh Med Res Counc Bull.* 2010 Dec;36(3):82-8.
147. Madhusudhan N, Basha PM, Rai P, Ahmed F, Prasad GR. Effect of maternal fluoride exposure on developing CNS of rats: protective role of Aloe vera, *Curcuma longa* and *Ocimum sanctum*. *Indian J Exp Biol.* 2010 Aug;48(8):830-6.
148. Lee HS, Li L, Kim HK, Bilehal D, Li W, Lee DS, et al. The protective effects of *Curcuma longa* Linn. extract on carbon tetrachloride-induced hepatotoxicity in rats via upregulation of Nrf2. *J Microbiol Biotechnol.* 2010 Sep;20(9):1331-8.
149. Hossen MS, Tanvir EM, Prince MB, Paul S, Saha M, Ali MY, et al. Protective mechanism of turmeric (*Curcuma longa*) on carbofuran-induced hematological and hepatic toxicities in a rat model. *Pharm Biol.* 2017 Dec;55(1):1937-1945. doi: 10.1080/13880209.2017.1345951.
150. Almalki E, Al-Shaebi EM, Al-Quarishy S, El-Matbouli M, Abdel-Baki AS. In vitro effectiveness of *Curcuma longa* and *Zingiber officinale* extracts on *Echinococcus protoscoleces*. *Saudi J Biol Sci.* 2017 Jan;24(1):90-94. doi: 10.1016/j.sjbs.2016.05.007. Epub 2016 May 14.
151. Nasai NB, Abba Y, Abdullah FF, Marimuthu M, Tijjani A, Sadiq MA, et al. In vitro larvicidal effects of ethanolic extract of *Curcuma longa* Linn. on *Haemonchus* larval stage. *Vet World.* 2016 Apr;9(4):417-20. doi: 10.14202/vetworld.2016.417-420. Epub 2016 Apr 28.
152. Kalaivani K, Senthil-Nathan S, Murugesan AG. Biological activity of selected Lamiaceae and Zingiberaceae plant essential oils against the dengue vector *Aedes aegypti* L. (Diptera: Culicidae). *Parasitol Res.* 2012 Mar;110(3):1261-8. doi: 10.1007/s00436-011-2623-x. Epub 2011 Sep 1.
153. Tripathi AK, Prajapati V, Verma N, Bahl JR, Bansal RP, Khanuja SP, et al. Bioactivities of the leaf essential oil of *Curcuma longa* (var. ch-66) on three species of stored-product beetles (Coleoptera). *J Econ Entomol.* 2002 Feb;95(1):183-9.
154. Song WY, Choi JH. Korean *Curcuma longa* L. induces lipolysis and regulates leptin in adipocyte cells and rats. *Nutr Res Pract.* 2016 Oct;10(5):487-493. Epub 2016 Jul 29.
155. Natural Standard (US). Turmeric (*Curcuma longa*) [Internet]. Somerville (MA): Natural Standard; 2013 [updated 2013 Jul 24; cited 2013 July 24]. Available from <http://www.naturalstandard.com/databases/herbssupplements/turmeric.asp?#>
156. US Government Printing Office. Substances generally recognized as safe, in: Code of Federal Regulations, 21, section 182 [Internet]. Washington DC [Updated 2013 July 19; cited 2013 July 24] Available at: <http://ecfr.gpoaccess.gov/cgi/t/text/textidx?c=ecfr&=786bafc6f6343634bf79fcdca7061e1&rgn=div5&view=text&node=21:3.0.1.13&idno=21#21:3.0.1.13.1.2>
157. Braun L. p. 903.
158. de Jager P. Turmeric: The Ayurvedic Spice of Life [Internet]. Boulder (CO): OM Organics; c2003 [cited 2013 Jul 17]. Available from: <http://www.bioponic.com/pdfs/TurmericAyurveda.pdf>
159. European Medicines Agency, Committee on Herbal Medicinal Products (HMPC). Community Herbal Monograph on *Curcuma longa* L., rhizome 12 November 2009 [Internet].