The Golden Spice: Health Benefits of Turmeric in Food

CHAPTER 30

SEHAR RAZZAQ[1], KANZA[2], ARIBA SADIA[2], ASFA KARAM[3]

[1]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan
[2]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan
[3]Department of Food Science and Human Nutrition, University of Veterinary and Animal Sciences, Lahore, Pakistan
[*]Corresponding author: sehar11298@gmail.com

SUMMARY

Turmeric (*Curcuma longa*) is an ancient herb that mainly grows throughout Asia, but primarily in China and India. Although the main route of its ingestion is the oral route, people can also apply it topically and inhale it as an Ayurvedic medicine. Regarding its composition, it has no cholesterol but is high in fiber and carbohydrates. Curcumin also contains small amounts of protein and fat. Except for forming salts when combined with phthalates and citrates, it is not extremely reactive with many other compounds. Due to this reason, turmeric is used in food to impart color and serve as a preservative. Turmeric is a powerful anti-inflammatory agent that can fight against inflammation by minimizing oxidative stress and free radical formation in the body. Studies have been demonstrated that the essential oil of turmeric leaves significantly inhibits the growth of fungi and the production of aflatoxins B1 and G1. The nano-curcumin helps in breaking the cell wall of the bacteria, resulting in their total extinction. It also regulates metabolic processes. Curcumin is useful against liver effects, anxiety and depression. Additionally, turmeric is beneficial against SARS-CoV-2. This chapter highlights the health benefits of turmeric in terms of its potential role as a food preservative, Anti-inflammatory, Anticarcinogenic, Antimicrobial, Antiarthritis, Antiviral and Anti-asthmatic agent. The nutritional composition, biological activity and toxicity of curcumin are also discussed.

INTRODUCTION

Turmeric (*Curcuma longa*) is a perennial herb that grows year after year and commonly found in many Asian countries, especially China and India. Turmeric belongs to the ginger family called Zingiberaceae. The plant's rhizome, which is used medicinally, produces a yellow powder. The root of the turmeric that provides curry powder and its distinctive yellow hue is dried. Turmeric is known by its several names, including Indian saffron, Haridra (Sanskrit, Ayurvedic), Jianghuang, Kyoo or Ukon (Japanese) and Curcum in the Arab world (Goel et al., 2008).

Asian cuisines have utilized turmeric for its taste and color, while Chinese and Ayurvedic medicine have employed it specifically as an anti-inflammatory and to treat jaundice, hematuria, bleeding, constipation and diarrhea. Turmeric is recognized for use in a broad range of medical applications and is included in the pharmacopoeia of China, Japan, and Korea, among other Asian nations. Turmeric is utilized topically to treat skin conditions including urticaria and consumed orally in China as well as for allergies, hepatitis virus, inflammatory joint disorders, sore throats and wounds. Turmeric is primarily administered orally, though it can also be applied topically, inhaled (according to Ayurvedic practice) or both. For the management of insect bites, parasitic infections, bleeding, eczema, wounds, boils, bruising, blistering, ulcers and skin conditions like herpes, zoster and pemphigus (WHO, 1999). Curcumin a yellow pigment which is extracted from *C. longa* L. (turmeric rhizomes) is the biological active ingredient of turmeric (Berretta et al., 2017; Nelson et al., 2017).

NUTRITIONAL COMPOSITION OF TURMERIC

Turmeric is high in fiber, carbohydrates and a small amount of protein and fat, yet it has no cholesterol at all. Furthermore, it also contains sufficient amounts of potassium, calcium, magnesium, phosphorus, vitamin C, pyridoxine and other nutrients. It is said that this is a naturally occurring food product with high nutritional value. Table 1 shows the nutritional makeup of turmeric in brief.

HISTORY OF TURMERIC USE

Turmeric usage in cooking and dyeing back over 4,000 years to India's Vedic era, when its vivid yellow hue and fragrant aroma led to its early use as a culinary spice and dye. In addition, turmeric also has a spiritual meaning. According to Hinduism, turmeric was first associated with South East Asian nations in 700 AD and then it moved to West and East

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Table 1. Percentage (%) of chemical constituents available in Turmeric (Ikpeama et al., 2014)

Constituents	Quantity present per 100g
Carbohydrates	67.38±0.01
Protein	9.40±0.02
Fat	6.85±0.00
Ash	2.85±0.02
Water	8.92±0.02
Ascorbic acid	0.05g/100g
Calcium	0.21±0.01
Potassium	0.46±0.03
Phosphorus	0.63±0.02
Riboflavin	0.59±0.02

African nations in 800-1200 AD. In many of these nations and areas, turmeric is now a widely grown seed. In addition to its long history of use, the role of turmeric in traditional medicine, particularly in Ayurveda and traditional Chinese medicine is very significant (Kocaadam & Şanlier, 2017). In these systems, this herb was used as a cure for a wide range of conditions, from straightforward illnesses to more complicated chronic conditions, including respiratory, cardiovascular and hepatic disorders, as well as simple ailments like dyspepsia, abdominal pain, bloating, sinusitis, and asthma (Aggarwal et al., 2007; Verma et al., 2018; Sanidad et al., 2019). However, despite being brought to Europe by Arab traders in the 13th century, turmeric is still considered a minor spice in Western nations.

Turmeric is well-known as a nutritional supplement and nutraceutical compound which makes turmeric one of the best-selling natural health products in the US since 2013. Turmeric has gained significant interest due to recent studies demonstrating its therapeutic role against COVID-19 for its potential to control cytokine-created damage (Valizadeh et al., 2020; Emirik, 2020).

Production and Use of Turmeric as a Food Additive

Turmeric is commonly added to foods to give color. *C. longa* is used in various foods in different amounts, from 5 to 500 mg/kg, depending on the type of food. When added to food, curcumin remains stable even when heated or in dry foods. Turmeric may not react much with other ingredients except it can form salts with phthalates and citrates. Turmeric is also not able to give a reaction with phosphates, chlorides, or bicarbonates. Apart from coloring food, curcumin is a powerful antioxidant. Turmeric helps to stop lipid peroxidation, which is harmful to our bodies. The antioxidant power of curcumin comes from its specific chemical structure with double carboxyl groups and hydroxyl groups.

Turmeric can capture harmful free radicals in our bodies, converting them into harmless substances that are safe for human health. When used as a food additive, turmeric slows down the oxidation of linoleic acid by about 80% (Jayaprakasha et al., 2006). Turmeric performs its role by releasing hydrogen ions and reducing free radicals (Wei et al., 2006). Turmeric can also neutralize hydrogen peroxide better than other common antioxidants like BHA, BHT or vitamin E. In high-cholesterol diets, curcumin can reduce oxidative stress in the liver by lowering the level of liver enzymes that cause oxidative stress and inflammation like catalase, glutathione peroxidase and superoxide dismutase (Ak & Gülçin, 2008).

Turmeric helps in heart disease by reducing inflammation-causing compounds such as TNF-α and IL-6 (Hussein et al., 2016). For people with high cholesterol, Curcumin supplements help in lowering the risk of cardiovascular problems. Turmeric also has a role in protecting against the oxidation of low-density lipoproteins, which can lead to conditions like thrombosis and arteriosclerosis (Mahfouz et al., 2009). In studies on asthmatic mice, Curcumin reduced lung inflammation by decreasing the expression of inflammatory molecules through a specific signaling pathway (Liu et al., 2015). Fig. 1 shows the health benefits of Turmeric.

ANTI-INFLAMMATORY AGENT

The role of stress produced by oxidative agents and its effective pathogenic processes are intimately associated with inflammation in many human chronic disorders. A well-known phenomenon is that inflammatory cells are responsible for producing several free radicals at a place where they produce inflammation in the human body, which causes inflammatory reactions and demonstrates the connection between oxidative stress and inflammation (Biswas, 2016).

Furthermore, a large number of reactive oxygen (ROS) along with nitrogen species may start a process inside the cells which involves an intracellular signaling cascade that enhances the production of pro-inflammatory genes. Inflammation has been linked to the development of several cancer forms (Jurenka, 2009). While TNF is thought to be the most potent NF-B stimulator, NF-B also controls TNF expression, which is in turn triggered by a variety of disease-causing viruses, gram-negative bacteria and most inflammatory cytokines. TNF is described as an important factor that regulates inflammation in most disorders, but its effect is only regulated by the stimulation of the nuclear factor (NF-B) transcription factor. Curcumin boosts the mode of action of nuclear factor B as a possible anti-inflammatory factor and has the ability to prevent its activation and then causing inflammation (Panahi et al., 2016).

ANTI-CARCINOGENIC PROPERTIES

Globally, various cancer types account for approximately 25% of all deaths. The drivers of cancer are genetic and epigenetic modifications that lead to apoptosis, unchecked tumor growth, metastasis and angiogenesis (Duvoix et al., 2005; Belt et al., 2012). Recent studies have shown that curcumin has a protective effect against cancer, with notable advancements being made in the treatment of lung, breast and gastrointestinal cancers. Many investigations for cancer therapy have documented that the properties of curcumin include its effectiveness against cancer occurrence, either by itself or in conjunction with conventional chemotherapeutic drugs (Bayomi et al., 2015).

Experiments conducted *in vivo* and *in vitro* have also demonstrated that turmeric inhibits the formation of tumors and angiogenesis, hence preventing carcinogenesis (Rubagotti et al., 2017). Sulfone, which is present in curcumin aptamers,

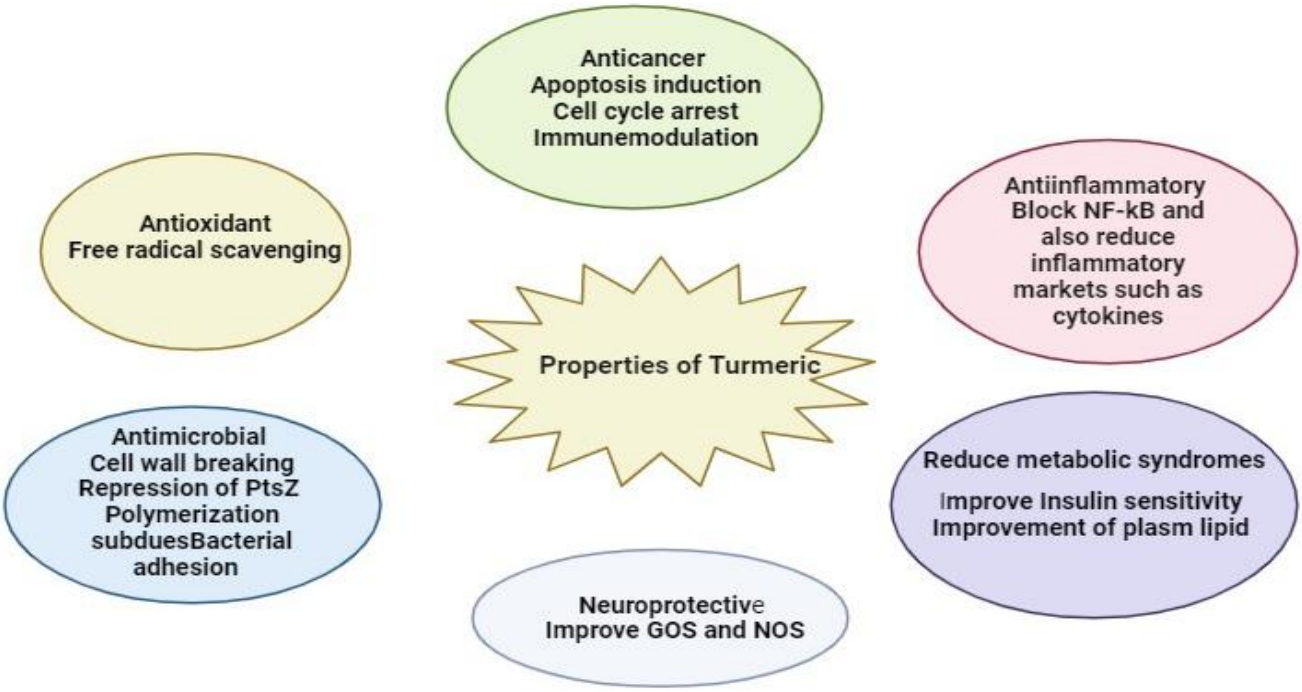

Fig 1. Summary of health benefits of turmeric

significantly decreases the growth of tumors in the human pancreatic, colon, prostate and lung (Allegra et al., 2017). Through a mechanism that depends on P53, curcumin can also cause cancer cells to undergo apoptosis. P53 is a significant tumor suppressor protein that influences DNA damage, apoptosis, and cell proliferation (Kandoth et al., 2013).

Numerous investigations have demonstrated a relationship between P53, and mRNAs linked to cancer (Hermeking, 2007; Ye et al., 2015). Additionally, Ye et al. (2015) demonstrated the proapoptotic action of curcumin relies on miR-192-5p and miR-215, which in non-small cell lung cancer activates the P53. Additional research has demonstrated that in HT-29 which are colon cancer cells present in colon cancer, to eliminate them curcumin-induced apoptosis is required which is p53-independent (Watson et al., 2010).

ANTI-METABOLIC SYNDROME PREVENTION

The idea that turmeric can reduce systemic inflammation extends beyond arthritis and is directly related to the health of many systems. One such condition is metabolic syndrome, which is characterized by resistance against the insulin hormone, high blood glucose level, high blood pressure, cholesterol, high level of triglyceride and obesity, particularly obesity of visceral organs.

Turmeric has been demonstrated to prevent multiple forms of cardiovascular disease by increasing insulin sensitivity (Chuengsamarn et al., 2012) decreasing adipogensis (Bradford, 2013), lowering blood pressure (Hlavackova et al., 2011), reducing inflammation (Sahebkar, 2014) and oxidative stress (Ak & Gulcin, 2008). According to recent research, turmeric influences the expression of genes and enzymes involved in lipid metabolism, which in turn causes plasma levels of cholesterol and triglycerides to drop while lipoprotein levels rise (DiSilvestro et al., 2012; Mohammadi et al., 2013). Additionally, obesity and over weight are associated with decreased levels of chronic inflammation, while pro-inflammatory cytokines are said to be produced as well. However, specific mechanisms are unknown. It is believed that these cytokines have played a central role in the complications associated with diabetes and cardiovascular disease (Na et al., 2013).

ANTI-INFLAMMATORY ACTIVITY

Studies have shown that turmeric has anti-inflammatory properties which is shown both in in vitro and in vivo studies. Studies have shown that turmeric's anti-inflammatory activity proves beneficial in decreasing pro-inflammatory transcription factors such as NF-KB and AP-1. This also proves its effect in reducing the pro-inflammatory cytokines including TNFα, IL-1b, IL-2, IL-6, IL-8, MIP-1a, MCP-1, C reactive protein and PGE2. Turmeric has a beneficial effect in down-regulating enzyme activity such as 5-lipoxygenase, COX-2 and COX-5 which inhibit the mitogen-activated protein kinases (MAPK) and pathways involved in nitric oxide synthase enzyme synthesis (Aggarwal et al., 2005).

Conversely, a strong correlation between antioxidant molecules and their anti-inflammatory properties is emerging as oxidative stress is known to initiate chronic inflammation. Turmeric can similarly affect the expression of NF-κB in this way. Proinflammatory cytokines including TNFα and interleukin (IL-1, IL-2, IL-6, and IL-8) are produced when the NF-κB pathway is activated and these cytokines are known to activate proinflammatory signaling pathways. Furthermore, curcumin may reduce inflammation and oxidative stress via activating the Nrf2 pathway. Prostaglandins and thromboxanes are produced from arachidonic acid via the COX pathway, which involves the COX isoenzymes i.e COX-

1 and COX-2. Turmeric has been shown in numerous studies to decrease the activation of COX-2 gene expression. In particular, COX-2 is activated through a large number of cytokines and tumor promoters, making it strongly associated with inflammation process and carcinogenic mechanisms.

ANTIMICROBIAL EFFECTS

For potentially fatal bacterial infections, turmeric is an antibacterial agent (Mythri & Bharath, 2012). Turmeric leaf essential oil has been shown to dramatically inhibit fungus growth and the generation of their aflatoxins B1 and G1. Despite being a very potent substance, turmeric's low water solubility limits its uses. The bacteria are killed off completely by the nano-curcumin, which ruptures the cell wall (Ji & Shen, 2014). Turmeric and *Epigallocatechin gallate* have the potential to be used in medication to treat or prevent *Acinetobacter baumannii* infections (Mythri et al., 2011). Because *Acanthamoeba (A.) castellanii* resists anti-amoebic medications, its removal is a challenging task. On *A. castellanii* cysts, ethanol extracts of plant varieties, such as daffodil, groundnut and turmeric, have been assessed against the killing of amoeba. The extract's ability to prevent Acanthamoeba cyst reproduction was verified by the scientists, albeit the effect varied in time and dose (Harish et al., 2010). Furthermore, gingivitis and plaque can be successfully avoided with a mouthwash infused with turmeric. Moreover, it has been discovered that using turmeric mouthwash greatly reduces the overall bacteria count (Wang et al., 2010). Turmeric also restricts the formation of temperature-sensitive Z mutants (Fts Z) by inhibiting the polymerization of Fts Z, which in turn prevents *Bacillus subtilis* and *Escherichia coli* from growing (Yanagisawa et al., 2015). Additionally, turmeric reduces cell proliferation and infectivity in a dose-dependent manner. Because it stops *Vibrio (V.) vulnificus* from growing, it significantly lessens the cytotoxicity of *V. vulnificus* for HeLa cells. Turmeric inhibits the adherence of bacteria and when RTX toxin binds to host cells, it prevents actin aggregation and host cell rounding (Doggui et al., 2012).

Turmeric can reduce *V. vulnificus*, which causes translocation in certain HeLa cells and aberrant proliferation (Dohare et al., 2008). Additionally, turmeric has been shown to have a broad spectrum of anti-viral activity (Zhang et al., 2012). Numerous further research has been conducted regarding its various modes of action against HIV. It has been demonstrated that curcumin inhibits HIV-1 integrase (Kulkarni et al., 2012). Furthermore, the infection and replication of viral genes can be inhibited by this polyphenol and its analogs. Polyphenols block HIV-associated kinases, such as tyrosine kinase and HIV protease. Additionally, turmeric works in tandem with other medications. Notably, turmeric inhibits the redox activity of apyrimidinic/apurinic endonuclease-1. Many different genes and pathways are impacted as a result.

Curcumin has been shown to slow down the reproduction cycle of the herpes virus linked to Kaposi's sarcoma and ultimately regulate the ensuing pathological processes such as angiogenesis (Sindhu et al., 2011; Kulkarni et al., 2012). Researchers have also documented the anti-influenza properties of the organic components found in the turmeric plant (Bhawana et al., 2011). By preventing the influenza-A virus's (IAV) adsorption and reproduction, it can combat the virus (Betts & Wareham, 2014).

ANTI-ARTHRITIS PROPERTIES

One chronic inflammatory condition that is thought to be caused by synovial fibroblast hyperplasia is rheumatoid arthritis. The strong anti-inflammatory and anti-arthritic effects of turmeric are well established (Sayed et al., 2012). Patients with active rheumatoid arthritis received real-time turmeric treatment and their outcomes were compared to those of the diclofenac sodium reference group. When compared to the individuals who are taking diclofenac sodium and those who are taking turmeric, the turmeric group has shown the most overall percentage improvement in reducing rheumatoid arthritis and these values have improved significantly (Waghmare et al., 2011). It was discovered that, in comparison to the diclofenac sodium group, the curcumin group was not harmful but proved healthful. It is thought that the anti-inflammatory, immune-suppressive, antioxidant and proliferative properties of turmeric contribute to the improvement of rheumatoid arthritis patients' symptoms (Kaur & Saraf, 2011).

ANTI-VIRAL PROPERTIES

Curcumin can treat a variety of viruses, including Papillomavirus (HPV), Hepatitis B virus (HBV), coxsackievirus, influenza virus, Hepatitis C virus (HCV), adenovirus, Human norovirus (HuNoV), Respiratory syncytial virus (RSV), and Herpes simplex 1 (HSV-1). Graphene oxide, which is included in turmeric has a synergistic antiviral effect on respiratory syncytial virus infections. Infants' lower respiratory tracts are home to the respiratory syncytial virus (RSV), which causes serious lung illness. Additionally, curcumin exhibits dose-dependent antiviral activity (Na et al., 2011). Curcumin inhibits the enzyme isosine-monophosphate dehydrogenase (IMPDH) in a non-competitive or competitive way. Rather than viral RNA replication, curcumin is present throughout viral entrance or other life cycle stages. Therefore, IMPDH should be suppressed for curcumin to potentially have antiviral, antiproliferative and antiparasitic actions (Na et al., 2013).

ANTI-ASTHMA AND ANTI-DIABETIC PROPERTIES

Turmeric helps with cold, runny nose and cough symptoms. It also makes it easier to breathe through the nose. Turmeric does this by increasing certain molecules in the body like IL-10 and IL-4, which help fight allergies. It also protects against asthma and reduces irritation in the airways (Fu et al., 2015). Turmeric is also good for diabetes because it has antioxidants. These antioxidants can reduce damage caused by diabetes, such as problems with blood vessels. Turmeric can also fight harmful substances such as ROS, which can damage cells. Recent studies have shown that turmeric is very good at this function (Sayer, 2015). Turmeric's ability to activate protective enzymes like heme oxygenase-11 (HO-1) helps to

prevent cell damage from oxidative stress. This can be especially helpful for people with diabetes (Siegel et al., 2014; Zhang et al., 2016).

Many studies, including animal, clinical and experimental ones, show that curcumin is a pleiotropic substance that interacts with a wide range of targets, such as nuclear factor E2-related factor (Nrf2), PKC, c-Jun N-terminal kinase (JNK), and peroxisome proliferator-activated receptor gamma (PPARγ). Curcumin has been demonstrated in clinical trials to help diabetics with their dyslipidemia, insulin resistance and blood glucose levels. Additionally, curcumin reduces oxidative stress, apoptosis and inflammatory activation, all of which are favorable in diabetes and DCM via several signaling channels. Diabetic neuropathy is an additional problem linked to this disease. According to Kapoor (2012), curcumin reduces pain related to depression, mitigates diabetic neuropathic pain, delays the onset of diabetic neuropathy and lessens postsurgical allodynia.

NEUROPROTECTIVE EFFECTS

The incidence rate of neurodegenerative disorders affecting millions of individuals globally increases including major depression, epilepsy, Parkinson's and Alzheimer's diseases. Chronic inflammation known as "neurodegeneration" is caused by alterations in the metabolism of neurons. Microglia and astrocyte activation enhance neuronal death in neuroinflammatory conditions. The latter are in charge of releasing proinflammatory cytokines including IL-1 and TNFα. As turmeric has antioxidant, anti-inflammatory and anti-protein properties, it has been studied as a therapeutic agent for the cure of several neurological complications including dementia, Alzheimer's, Parkinson's disease, multiple sclerosis and Huntington's disease (Salehi et al., 2020).

Microglia and astrocyte activation enhances the neuronal death in neuroinflammatory conditions. The latter are in charge of releasing proinflammatory cytokines including IL-1 and TNFα. Several studies have been demonstrated that curcumin prevents activated microglia and astrocytes from producing prostaglandins and inflammatory cytokines (Cainciulli et al., 2016). The primary cause of AD is the build-up of plaques containing the amyloid-ß (Aß) peptide, which results from astrocytosis, microgliosis and the presence of proinflammatory chemicals in the brain (Chen et al., 2014).

In multiple sclerosis, an inflammation which is caused by autoimmune inflammatory disease mainly affects young adults and women through a mechanism known as demyelinatinglesions. Turmeric has also shown neuroprotective effects through different mechanisms, including antioxidant, anti-inflammatory and anti-proliferative. Curcumin also demonstrated the ability to regulate several molecular targets, including enzymes (COX-2, iNOS, OH-1, LOX) and transcriptional factors including NF-kB, Nrf2, AP-1, and STAT-1,-3,-4). It also demonstrate activities related to proteins (caspase-3,-9, Bcl-2, prostaglandin, CRP, myosin light chain), inflammatory cytokines (chemokine ligand, interleukin, TNFa), protein kinase (AK, JNK, JAK, MAPK) and growth factors and receptors such as TLRs, chemokine receptor, TGF-a, TGF-ß (Qureshi et al., 2018).

HEPATOPROTECTIVE PATHWAYS

Many substances are the main factors that are responsible for causing acute and chronic damage to the liver, such as fibrosis of the liver, non-alcoholic steatohepatitis, non-alcoholic liver disease and even cirrhosis. These substances include alcohol, drugs, pollutants, parasites and food ingredients. Hepatoprotective properties of turmeric have been well investigated (Tung et al., 2017; Macias-Perez et al., 2019).

According to Choudhury et al. (2016), a turmeric injection (8.98 µM) raised succinate dehydrogenase activity, GR and GST levels while decreasing NADH oxidase in Swiss albino rats with CCl4-induced hepatotoxicity. When curcumin (200 mg/kg) was administered to Sprague-Dawley rats for the same type of hepatotoxicity, the liver's glutathione level rose, lipid peroxidase level dropped, the activities of both aspartate aminotransferase (AST) and alanine transaminase (ALT) decreased. Therefore, curcumin, by lowering the levels of ALT, AST and alkaline phosphatase levels, raising GST, GR, GPx, SOD and CAT, and lowering NO while also blocking ROS formation (Fig. 2) may be a promising drug to prevent oxidative stress-related liver disease (Farzaei et al., 2018).

TURMERIC AGAINST SARS-CoV-2

The SARS-CoV-2 pandemic began in December 2019 and has since swiftly spread over the entire planet. Almost no particular medication or vaccination has been licensed for use as a cure or a prophylactic measure. Even though hydroxychloroquine, anti-retroviral pills and other treatments have been employed up to this point. There is evidence of the antiviral effects of certain curcumin derivatives. Five active derivative compounds of the turmeric additives decreased the activation of H1N1-induced neuraminidase in H1N1-infected lung epithelial cells, according to the stimulation assay of neuraminidase (Scannell et al., 2012). Tetramethyl curcumin and curcumin even further down-regulate the same nucleoprotein activation. By interfering with the action of infectious hemagglutination (HA), turmeric has also been shown to have significant antiviral activity against the H5N1 virus in Madin-Darby dog kidney (MDCK) cells in vitro. This could be helpful in situations where there has been a recent disease outbreak (Yu et al., 2015).

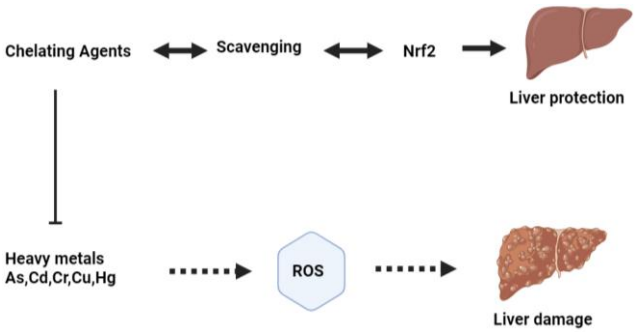

Fig 2. Effect of Turmeric against hepatic diseases

The effects of the anti-H5N1 virus infection with the help of turmeric extracts have been demonstrated (Bergman et al., 2013; Esmaily et al., 2015) with both the up-regulation of TNF-alpha and IFN-β mRNA expressions within the examined MDCK cells. Because turmeric inhibits HIV protease and integrase, it also helps with other viral issues including AIDS. Turmeric also inhibits the activity of other infections, including dengue, chikungunya, zika, hepatitis B and hepatitis C. Respiratory sickness syndrome with fulminant hypercytokinemia and multi-organ failure is the primary cause of COVID-19 fatality rates (Gupta et al., 2020). Curcumin has been proven effective in lessening influenza-related lung tissue damage by blocking NF-B signaling and then by decreasing the release of inflammatory cytokines (Lai et al., 2020). Table 2 summarizes the biological activities of turmeric and its compounds.

TURMERIC AGAINST CARDIOVASCULAR DISEASES

It has been established that the inflammatory process is the main culprit for the development of cardiovascular diseases (CVD). Through a number of methods, curcumin therapy is said to have an anti-inflammatory impact against CVD. It is claimed that curcumin activates the Nrf2-dependent antioxidant response element, hence enabling 1-OH expression. Additionally, study also states that curcumin promotes p21 expression through 1-OH and suppresses TNF-α in blood vessels and smooth muscle cells of the aorta (Pae et al., 2007; Wongcharoen & Phrommintikul, 2009).

Curcumin therapy helps in reducing ischemia in mice by activating the JAK2/STAT3 signal pathway (Duan et al., 2012). Additionally, curcumin has been shown to mitigate cirrhosis and liver fibrosis (Chen et al., 2014; Zhong et al., 2016). When curcumin was administered to Sprague-Dawley rats with CCl4-induced hepatic fibrosis, the extracellular matrix overproduction in HSCs was reduced, which in turn led to a decrease in liver fibrosis and PPAR-G activation upregulating PTEN and miR-29b expression, down-regulating cannabinoid receptors (CBR) type 1 and DNA methyltransferase altering the PDGF-R/ERK and mTOR pathways (Chen et al., 2014).

TURMERIC AGAINST FEMALE INFERTILITY

The primary cause of an-ovulatory infertility is PCOS (Teede et al., 2010). Studies on animals have suggested that curcumin may enhance ovarian function in PCOS patients. Treatment with nano curcumin resulted in thicker granulosa cells and the development of oocytes in rats with PCOS (Abuelezz et al., 2020). A different study found that the curcumin-treated group had a greater corpus luteum diameter and a much thinner theca layer when compared to the PCOS group (Mohammadi et al., 2017). Additionally, curcumin therapy showed outcomes similar to those of clomiphene citrate, the first-line treatment for anovulatory PCOS, with cysts disappearing and healthy follicles and corpora lutea appearing (Reddy et al., 2016). In contrast to the PCOS rat group, a different study discovered that 5.4/100mgg^{-1} of curcumin in nanoparticle form decreased the overall number of primary, secondary, antral and primordial follicles. These conflicting findings of curcumin's effects on ovarian follicles are expected given the many ways that PCOS is induced in animal models and the various forms of curcumin employed (Abhari et al., 2020).

TOXICITY AND SAFETY CONSIDERATIONS

Short-term studies showed that curcumin can be consumed about 8 g per day and does not show any signs of toxicity in humans. But the same condition does not apply to long-term studies because during these studies, human beings have shown that the consumption of turmeric from 1-4 months at a dose of 0.9-3.6 g per day results in adverse effects such as nausea and diarrhea. The level of serum enzymes such as alkaline phosphatase and lactate dehydrogenase enzymes also increases (Sharma et al., 2004).

An epidemiological study in India showed that people with a turmeric-rich diet of about 0.15 g per day have a lower risk of gastrointestinal cancers (Sharma et al., 2005). Long-term studies relating to it are less in humans, so this dose is considered safe. The dose of 0.15 g per day is deemed safe by WHO but should be less than 10 times what the suppliers of its supplements generally recommend. Unfortunately, studies regarding turmeric safety and toxicity have not been done so well but, despite all this, it is considered safe and highly efficient. The curcumin is a part of the diet so, this fact is not enough to prove its safety concerns. Many components of the human diet have shown their toxic effect when we use them as dietary supplements. Turmeric does not cause toxicity in short-term studies is not enough to prove its safety. For a drug to be completely safe its safety should be checked in long-term studies (Goodman et al., 2004).

ROUTES OF ADMINISTRATION OF CURCUMIN

Biocompatibility problems occur when curcumin has been administered intravenously, it should be administered at a very low dose than orally (Soleimani et al., 2018). It should be noted that curcumin may cause specific types of pharmacokinetic modifications to antibiotics, corticosteroids,

Table 2. Biological activity of turmeric and its compounds

Ingredients	Biological functions	Reference
Turmeric powder	working against inflammation, protozoal activity Anti-tumor, anti-protozoan, and help in wound-healing	Gujral et al., 1953
Methylcurcumin	Inhibit protozoal activity	Gomes et al., 2002
Demethoxycurcumin & Bisdemethoxycurcumin	Reduce oxidative stress	Unnikrishnan & Rao, 1995
Volatile oil	Antifungal, Antibacterial and Anti-inflammatory	Chandra & Gupta, 1972
Curcumin	Prove effectiveness against bacteria, protozoan, viruses and Abnormal cell growth.	Lutomski et al., 1974

antidepressants, chemotherapeutic treatments and cardiovascular medications. As such, it needs to be regularly provided in a concurrently accessible manner with other collectivist drugs (Bahramsoltani et al., 2017). Turmeric is administrated at a dose of around 1000 mg/kg body mass proves effective in a small reduction in weight and also an increase in F2 generation chicks (Sun et al., 2012). The same level of security of these contemporary mixes needs to be taken into consideration when interpreting drug transfer methods to increase the bioactivity of turmeric. For example, the product may be harmful if carriers or surfactants are utilized as part of a biocompatibility action plan (Gota et al., 2010). Although the majority of these cutting-edge technologies also happen to be safe, solid lipid curcumin formulation is not negatively impacted in either healthy populations or patients with osteosarcoma. The poly (N-isopropylacrylamide) distribution network is another alternative framework that delivers curcuminoids nasally to the brain, and it shows almost no toxicity (Ahmad et al., 2016).

Nanomaterials containing dipeptide curcumin are too safe. Alpha, beta-dehydro phenylalanine, and methionine are amino acids that are easily dissolved in nature and are used to create dipeptides. Furthermore, in HCT 116 tumor xenograft models, curcumin-loaded blood serum albumin nanoparticles exhibited almost no harmful effects when used intravenously (Kim et al., 2011). According to a recent intravenous curcumin trial, rabbits in the curcumin nanosuspension group were less likely than those in the curcumin solution group to experience local irritation, phlebitis, and erythrocyte hemolysis (Gao et al., 2011).

Turmeric is well-known around the world for its anti-inflammatory and antioxidant properties, as well as other possible advantages that could improve general health. It enhances bioavailability when combined with piperin and Turmeric. Additionally, oxidative, inflammatory, metabolic, arthritic, anxiety and hyperlipidemic illnesses may be treated with curcumin. Throughout rehabilitation and performance, sedentary people monitor and exacerbate inflammation and painful muscles caused by exercise (Peng et al., 2018).

Furthermore, it is helpful for those who have not yet received a successful medical diagnosis or treatment. The main ingredient in turmeric is the root, which has an abundance of vitamins, minerals, and bioactive chemicals that work to make it the safest medicinal herb. It is also used in nursing women who are experiencing renal or hepatic failure, as well as during pregnancy. The primary bioactive component is curcumin, which is present together with other compounds such as atlantone curcuminoid, dimethoxycurcumin, diarylheptanoid and diferuloylmethane flavonoid curcumin. These offer protection against many cellular damages due to their antibacterial, anti-inflammatory, and antioxidant properties (Porticos et al., 2016).

REFERENCES

Abhari SMF, R Khanbabaei, NH Roodbari et al., 2020. Curcumin-loaded super-paramagnetic iron oxide nanoparticle effects on apoptotic factors expression and histological changes in a prepubertal mouse model of polycystic ovary syndrome-induced by dehydroepiandrosterone-A molecular and stereological study. Life Sciences 249: 117515. https://doi.org/10.1016/j.lfs.2020.117515

Abuelezz NZ, ME Shabana, HM Abdel-Mageed et al., 2020. Nanocurcumin alleviates insulin resistance and pancreatic deficits in polycystic ovary syndrome rats: Insights on PI3K/AkT/mTOR and TNF-α modulations. Life Sciences 256:118003. https://doi.org/10.1016/j.lfs.2020.118003

Aggarwal BB, S Shishodia, Y Takada et al., 2005. Curcumin suppresses the paclitaxel-induced nuclear factor-κB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. Clinical Cancer Research 11:7490-8. https://doi.org/10.1158/1078-0432.CCR-05-1192

Ahmad N, I Ahmad, S Umar et al., 2016. PNIPAM nanoparticles for targeted and enhanced nose-to-brain delivery of curcuminoids: UPLC/ESI-Q-ToF-MS/MS-based pharmacokinetics and pharmacodynamic evaluation in cerebral ischemia model. Drug Delivery 23:2095-114. https://doi.org/10.3109/10717544.2014.941076

Ak T & Gülçin I, 2008. Antioxidant and radical scavenging properties of curcumin. Chemico-Biological Interactions 174:27-37. https://doi.org/10.1016/j.cbi.2008.05.003

Allegra A, V Innao, S Russo et al., 2017. Anticancer activity of curcumin and its analogues: preclinical and clinical studies. Cancer Investigation 35:1-22. https://doi.org/10.1080/07357907.2016.1247166

Bahramsoltani R, R Rahimi, MH Farzaei et al., 2017. Pharmacokinetic interactions of curcuminoids with conventional drugs: A review. Journal of Ethnopharmacology 209:22. https://doi.org/10.1016/j.jep.2017.07.022

Bayomi SM, HA El-Kashef, MB El-Ashmawy et al., 2015. Synthesis and biological evaluation of new curcumin analogues as antioxidant and antitumor agents: molecular modeling study. European Journal of Medicinal Chemistry 101:584-94. https://doi.org/10.1016/j.ejmech.2015.07.014

Belt EJT, RPM Brosens, PMD Diemen et al., 2012. Cell cycle proteins predict recurrence in stage II and III colon cancer. Annals of Surgical Oncology 19:682-92. https://doi.org/10.1245/s10434-012-2216-7

Bergman J, C Miodownik, Y Bersudsky et al., 2013. Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. Clinical Neuropharmacology 36:73-7. https://doi.org/10.1097/WNF.0b013e31828ef969

Berretta M, CD Pepa, P Tralongo et al., 2017. Use of Complementary and Alternative Medicine (CAM) in cancer patients: An Italian multicenter survey. Oncotarget 8:24401. https://doi.org/10.18632/oncotarget.14224

Betts JW & DW Wareham, 2014. In vitro activity of curcumin in combination with epigallocatechin gallate (EGCG) versus multidrug-resistant Acinetobacter baumannii. BMC Microbiology 14:172. https://doi.org/10.1186/1471-2180-14-172

Bhawana, RK Basniwal, HS Buttar et al., 2011. Curcumin nanoparticles: preparation, characterization, and antimicrobial study. Journal of Agricultural and Food Chemistry 59:2056-61. https://doi.org/10.1021/jf104402t

Biswas SK, 2016. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox?. Oxidative Medicine and Cellular Longevity 2016:5698931. https://doi.org/10.1155/2016/5698931

Bradford PG, 2013. Curcumin and obesity. Biofactors 39:78-87. https://doi.org/10.1002/biof.1074

Chandra D & SS Gupta, 1972. Antiinflammatory and antiarthritic activity of volatile oil of Curcuma longa (Haldi). Indian Journal of Medical Research 60:138-42.

Chen N, Q Geng, J Zheng et al., 2014. Suppression of the TGF-beta/Smad signaling pathway and inhibition of hepatic stellate cell proliferation play a role in the hepatoprotective effects of curcumin against alcohol-induced hepatic fibrosis. International Journal of Molecular Medicine 34:1110-6. https://doi.org/10.3892/ijmm.2014.1867

Choudhury ST, N Das, S Ghosh et al., 2016. Vesicular (liposomal and nanoparticulated) delivery of curcumin: a comparative study on carbon tetrachlori DiSilvestro RA de-mediated oxidative hepatocellular damage in rat model. International Journal of Nanomedicine 18:2179-93. https://doi.org/10.2147/IJN.S101886

Chuengsamarn S, S Rattanamongkolgul, R Luechapudiporn et al., 2012. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 35:2121-7. https://doi.org/10.2337/dc12-0116

Cianciulli A, R Calvello, C Porro et al., 2016. PI3k/Akt signalling pathway plays a crucial role in the anti-inflammatory effects of curcumin in LPS-activated microglia. International Immunopharmacology 36:282-90. https://doi.org/10.1016/j.intimp.2016.05.007

DiSilvestro RA, E Joseph, S Zhao et al., 2012. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutrition Journal 11:79. https://doi.org/10.1186/1475-2891-11-79

Doggui S, JK Sahni, M Arseneault et al., 2012. Neuronal uptake and neuroprotective effect of curcumin-loaded PLGA nanoparticles on the

human SK-N-SH cell line. Journal of Alzheimer's Disease 30:377-92. https://doi.org/10.3233/JAD-2012-112141

Dohare P, S Varma, M Ray et al., 2008. Curcuma oil modulates the nitric oxide system response to cerebral ischemia/reperfusion injury. Nitric Oxide 19:20. https://doi.org/10.1016/j.niox.2008.04.020

Duan W, Y Yang, J Yan et al., 2012. The effects of curcumin post-treatment against myocardial ischemia and reperfusion by activation of the JAK2/STAT3 signaling pathway. Basic Research in Cardiology 107:263. https://doi.org/10.1007/s00395-012-0263-7

Duvoix A, R Blasius, S Delhalle et al., 2005. Chemopreventive and therapeutic effects of curcumin. Cancer Letters 223:181-90. https://doi.org/10.1016/j.canlet.2004.09.041

El-Sayed NM, KA Ismail, SA Ahmed et al., 2012. In vitro amoebicidal activity of ethanol extracts of *Arachis hypogaea* L., *Curcuma longa* L. and *Pancratium maritimum* L. on *Acanthamoeba castellanii* cysts. Parasitology Research 110:1985-92. https://doi.org/10.1007/s00436-011-2727-3

Emirik M, 2022. Potential therapeutic effect of turmeric contents against SARS-CoV-2 compared with experimental COVID-19 therapies: in silico study. Journal of Biomolecular Structure and Dynamics 40:2024-37. https://doi.org/10.1080/07391102.2020.1835719

Esmaily H, A Sahebkar, M Iranshahi et al., 2015. An investigation of the effects of curcumin on anxiety and depression in obese individuals: A randomized controlled trial. Chinese Journal of Integrative Medicine 21:332-8. https://doi.org/10.1007/s11655-015-2160-z

Farzaei MH, M Zobeiri, F Parvizi et al., 2018. Curcumin in liver diseases: a systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients 10:855. https://doi.org/10.3390/nu10070855

Fu W, W Zhuang, S Zhou et al., 2015. Plant-derived neuroprotective agents in Parkinson's disease. American Journal of Translational Research 7:1189.

Gao Y, Z Li, M Sun et al., 2011. Preparation and characterization of intravenously injectable curcumin nanosuspension. Drug Delivery 18:131-42. https://doi.org/10.3109/10717544.2010.520353

Goel A, AB Kunnumakkara, BB Aggarwal et al., 2008. Curcumin as "Curecumin": From kitchen to clinic. Biochemical Pharmacology 75:787-809. https://doi.org/10.1016/j.bcp.2007.08.016

Gomes DCF, LV Alegrio, MEF de Lim et al., 2002. Synthetic derivatives of curcumin and their activity against *Leishmania amazonensis*. Arzneimittel for Schung 52:120-4. https://doi.org/10.1055/s-0031-1299867

Goodman GE, MD Thornquist, J Balmes et al., 2004. The beta-carotene and retinol efficacy trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping betacarotene and retinol supplements. Journal of the National Cancer Institute 96: 1743-50. https://doi.org/10.1093/jnci/djh320

Gota VS, GB Maru, TG Soni et al., 2010. Safety and pharmacokinetics of a solid lipid curcumin particle formulation in osteosarcoma patients and healthy volunteers. Journal of Agricultural and Food Chemistry 58:2095-9. https://doi.org/10.1021/jf9024807

Gujral ML, NK Chowdhury, PN Saxena et al., 1953. The effect of certain indigenous remedies on the healing of wounds and ulcers. Journal of Indian State Medical Association 22:273-6.

Gupta H, M Gupta, S Bhargava et al., 2020. Potential use of turmeric in COVID-19. Clinical and Experimental Dermatology 45:902-3. https://doi.org/10.1111/ced.14357

Harish G, C Venkateshappa, RB Mythri et al., 2010. Bioconjugates of curcumin display improved protection against glutathione depletion mediated oxidative stress in a dopaminergic neuronal cell line: implications for Parkinson's disease. Bioorganic & Medicinal Chemistry 18:2631-8. https://doi.org/10.1016/j.bmc.2010.02.029

Hermeking H, 2007. p53 enters the microRNA world. Cancer Cell 12:414-8. https://doi.org/10.1016/j.ccr.2007.10.028

Hlavačková L, A Janegová, O Uličná et al., 2011. Spice up the hypertension diet-curcumin and piperine prevent remodeling of aorta in experimental L-NAME induced hypertension. Nutrition & Metabolism 8:72. https://doi.org/10.1186/1743-7075-8-72

Hussein SA, YAF El Senosi, MRR Hassanien et al., 2016. Ameliorative effect of curcumin on hepatic oxidative stress, antioxidant status, cardiac markers enzymes and inflammation in high cholesterol diet- induced hypercholesterolemia in rats. International Journal of Pharmacology 6:1496-505.

Ikpeama A, GI Onwuka, C Nwankwo et al., 2014. Nutritional composition of tumeric (*Curcuma longa*) and its antimicrobial properties. International Journal of Scientific and Engineering Research 5:1085-9.

Jayaprakasha GK, LJ Rao, KK Sakariah et al., 2006. Antioxidant activities of curcumin, demethoxycurcumin and bisdemethoxycurcumin. Food Chemistry 98:720-4. https://doi.org/10.1016/j.foodchem.2005.06.037

Ji HF & L Shen, 2014. The multiple pharmaceutical potential of curcumin in Parkinson's disease. CNS & Neurological Disorders-Drug Targets 13:369-73. https://doi.org/10.2174/18715273113129990077

Jurenka JS, 2009. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative Medicine Review 14:141-53.

Kandoth C, MD Mclellan, F Vandin et al., 2013. Mutational landscape and significance across 12 major cancer types. Nature 502:333-9. https://doi.org/10.1038/nature12634

Kapoor S, 2012. Curcumin and its emerging role in pain modulation and pain management. The Korean Journal of Pain 25:202-3. https://doi.org/10.3344/kjp.2012.25.3.202

Kaur CD & S Saraf, 2011. Topical vesicular formulations of *Curcuma longa* extract on recuperating the ultraviolet radiation-damaged skin. Journal of Cosmetic Dermatology 10:260-5. https://doi.org/10.1111/j.1473-2165.2011.00586.x

Keshavarzi Z, F Shakeri, GE Barreto et al., 2019. Medicinal plants in traumatic brain injury: Neuroprotective mechanisms revisited. Biofactors 45:517-35. https://doi.org/10.1002/biof.1516

Kim TH, HH Jiang, YS Youn et al., 2011. Preparation and characterization of water-soluble albumin-bound curcumin nanoparticles with improved antitumor activity. International Journal of Pharmaceutics 403:285-91. https://doi.org/10.1016/j.ijpharm.2010.10.041

Kocaadam B & N Şanlier, 2017. Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. Critical Reviews in Food Science and Nutrition 57:2889-95. https://doi.org/10.1080/10408398.2015.1077195

Kulkarni SK, KK Akula, J Deshpande et al., 2012. Evaluation of antidepressant-like activity of novel water-soluble curcumin formulations and St. John's wort in behavioral paradigms of despair. Pharmacology 89:83-90. https://doi.org/10.1159/000335660

Lai Y, Y Yan, S Liao et al., 2020. 3D-quantitative structure-activity relationship and antiviral effects of curcumin derivatives as potent inhibitors of influenza H1N1 neuraminidase. Archives of Pharmacal Research 43:489-502. https://doi.org/10.1007/s12272-020-01230-5

Liu L, Y Shang, M Li et al., 2015. Curcumin ameliorates asthmatic airway inflammation by activating nuclear factor-E2-related factor 2/haem oxygenase (HO)-1 signalling pathway. Clinical and Experimental Pharmacology and Physiology 42:520-9. https://doi.org/10.1111/1440-1681.12384

Lutomski J, B Kedzia, W Debska et al., 1974. Effect of an alcohol extract and of active ingredients from Curcuma longa on bacteria and fungi. Planta Medica 26:9-19. https://doi.org/10.1055/s-0028-1097963

Macías-Pérez JR, BJ Vázquez-López, MH Muñoz-Ortega et al., 2019. Curcumin and α/β-adrenergic antagonists cotreatment reverse liver cirrhosis in hamsters: participation of Nrf-2 and NF-κB. Journal of Immunology Research 2019:319794. https://doi.org/10.1155/2019/3019794

Mahfouz MM, SQ Zhou, FA Kummerow et al., 2009. Curcumin prevents the oxidation and lipid modification of LDL and its inhibition of prostacyclin generation by endothelial cells in culture. Prostaglandins & other Lipid Media 90:13-20. https://doi.org/10.1016/j.prostaglandins.2009.06.005

Mohammadi A, A Sahebkar, M Iranshahi et al., 2013. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytotherapy Research 27:374-9. https://doi.org/10.1002/ptr.4715

Mohammadi S, P Kayedpoor, L Karimzadeh-Bardei et al., 2017. The effect of curcumin on TNF-α, IL-6 and CRP expression in a model of polycystic ovary syndrome as an inflammation state. Journal of Reproduction & Infertility 18:352-60.

Mythri RB & MMS Bharath, 2012. Curcumin: a potential neuroprotective agent in Parkinson's disease. Current Pharmaceutical Design 18:91-9. https://doi.org/10.2174/138161212798918995

Mythri RB, J Veena, G Harish et al., 2011. 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. British Journal of Nutrition 106:63-72. https://doi.org/10.1017/S0007114510005817

Na HS, MH Cha, DR Oh et al., 2011. Protective mechanism of curcumin against Vibrio vulnificus infection. FEMS Immunology & Medical Microbiology 63:355-62. https://doi.org/10.1111/j.1574-695X.2011.00855.x

Na LX, Y Li, HZ Pan et al., 2013. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: A double-blind, placebo-controlled trial. Molecular Nutrition & Food Research 57:1569-77. https://doi.org/10.1002/mnfr.201200131

Nelson KM, JL Dahlin, J Bisson et al., 2017. The essential medicinal chemistry of curcumin: miniperspective. Journal of Medicinal Chemistry 60:1620-37. https://doi.org/10.1021/acs.jmedchem.6b00975

Pae HO, GS Jeong, SO Jeong et al., 2007. Roles of heme oxygenase-1 in curcumin-induced growth inhibition in rat smooth muscle cells. Experimental & Molecular Medicine 39:267-77. https://doi.org/10.1038/emm.2007.30

Panahi Y, MS Hosseini, N Khalili et al., 2016. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomedicine & Pharmacotherapy 82:578-82. https://doi.org/10.1016/j.biopha.2016.05.037

Peng X, C Dai, Q Liu et al., 2018. Curcumin attenuates on carbon tetrachloride-induced acute liver injury in mice via modulation of the Nrf2/HO-1 and TGF-β1/Smad3 pathway. Molecules 23:215. https://doi.org/10.3390/molecules23010215

Portincasa P, L Bonfrate, MLL Scribano et al., 2016. Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. Journal of Gastrointestinal & Liver Diseases 25:151-7. https://doi.org/10.15403/jgld.2014.1121.252.ccm

Qureshi M, EA Al-Suhaimi, F Wahid et al., 2018. Therapeutic potential of curcumin for multiple sclerosis. Neurological Sciences 39:207-14. https://doi.org/10.1007/s10072-017-3149-5

Reddy PS, N Begum, S Mutha et al., 2016. Beneficial effect of curcumin in letrozole induced polycystic ovary syndrome. Asian Pacific Journal of Reproduction 5:116-22. https://doi.org/10.1016/j.apjr.2016.01.006

Rubagotti S, S Croci, E Ferrari et al., 2017. Uptake of Ga-curcumin derivatives in different cancer cell lines: Toward the development of new potential 68Ga-labelled curcuminoids-based radiotracers for tumour imaging. Journal of Inorganic Biochemistry 173:113-9. https://doi.org/10.1016/j.jinorgbio.2017.05.002

Sahebkar A, 2014. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytotherapy Research 28:633-42. https://doi.org/10.1002/ptr.5045

Salehi B, MLD Prado-Audelo, H Cortés et al. 2020. Therapeutic applications of curcumin nanomedicine formulations in cardiovascular diseases. Journal of Clinical Medicine 9:746. https://doi.org/10.3390/jcm9030746

Sanidad KZ, E Sukamtoh, H Xiao et al., 2019. Curcumin: recent advances in the development of strategies to improve oral bioavailability. Annual Review of Food Science & Technology 10:597-617. https://doi.org/10.1146/annurev-food-032818-121738

Sayer A, 2015. Yeast is a cause of cancer and turmeric can kill both. research confirms. Research 4:339.

Scannell JW, A Blanckley, H Boldon et al., 2012. Diagnosing the decline in pharmaceutical R&D efficiency. Nature Reviews Drug Discovery 11:191-200. https://doi.org/10.1038/nrd3681

Sharma RA, SA Euden, SL Platton et al., 2014. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clinical Cancer Research 10:6847-54. https://doi.org/10.1158/1078-0432.CCR-04-0744

Siegel R, J Ma, Z Zou et al., 2014. Cancer statistics, 2014. Cancer Journal for Clinicians 64:9-29. https://doi.org/10.3322/caac.21208

Sindhu K, R Indra, A Rajaram et al., 2011. Investigations on the interaction of gold-curcumin nanoparticles with human peripheral blood lymphocytes. Journal of Biomedical Nanotechnology 7:56. https://doi.org/10.1166/jbn.2011.1199

Soleimani V, A Sahebkar, H Hosseinzadeh et al., 2018. Turmeric (*Curcuma longa*) and its major constituent (curcumin) as nontoxic and safe substances. Phytotherapy Research 32:985-95. https://doi.org/10.1002/ptr.6054

Sun M, X Su, B Ding et al., 2012. Advances in nanotechnology-based delivery systems for curcumin. Nanomedicine 7:1085-100. https://doi.org/10.2217/nnm.12.80

Teede H, A Deeks, L Moran et al., 2010. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Medicine 8:41. https://doi.org/10.1186/1741-7015-8-41

Tung BT, NT Hai, PK Son et al., 2017. Hepatoprotective effect of phytosome curcumin against paracetamol-induced liver toxicity in mice. Brazilian Journal of Pharmaceutical Sciences 53:16136. https://doi.org/10.1590/s2175-97902017000116136

Unnikrishnan MK & MN Rao, 1995. Inhibition of nitric-induced oxidation of hemoglobin by curcuminoids. Pharmazie 50:490-2.

Valizadeh H, S Abdolmohammadi-Vahid, S Danshina et al., 2020. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. International Immunopharmacology 89:107088. https://doi.org/10.1016/j.intimp.2020.107088

Verma RK, P Kumari, RK Maurya et al., 2018. Medicinal properties of turmeric (*Curcuma longa* L.): a review. International Journal of Chemical Studies 6:1354-7.

Waghmare PF, AU Chaudhari, VM Karhadkar et al., 2011. Comparative evaluation of turmeric and chlorhexidine gluconate mouthwash in prevention of plaque formation and gingivitis: A clinical and microbiological study. Journal of Contemporary Dental Practice 12:221-4. https://doi.org/10.5005/jp-journals-10024-1038

Wang R, YH Li, Y Xu et al., 2010. Curcumin produces neuroprotective effects via activating brain-derived neurotrophic factor/TrkB-dependent MAPK and PI-3K cascades in rodent cortical neurons. Progress in Neuro-Psychopharmacology and Biological Psychiatry 34:147-153. https://doi.org/10.1016/j.pnpbp.2009.10.016

Watson JL, R Hill, PB Yaffe et al., 2010. Curcumin causes superoxide anion production and p53-independent apoptosis in human colon cancer cells. Cancer Letters 297:18. https://doi.org/10.1016/j.canlet.2010.04.018

Wei QY, WF Chen, B Zhou et al., 2006. Inhibition of lipid peroxidation and protein oxidation in rat liver mitochondria by curcumin and its analogues. Biochimica Biophysica Acta 1760:70-7. https://doi.org/10.1016/j.bbagen.2005.09.008

WHO, 1999. Rhizoma Curcumae Longae, WHO monographs on selected medicinal plants Vol 1: World Health Organisation 1999.

Wise R, T Hart, O Cars et al., 1998. Antimicrobial resistance. BMJ 317:609. https://doi.org/10.1136/bmj.317.7159.609

Wongcharoen W & A Phrommintikul, 2009. The protective role of curcumin in cardiovascular diseases. International Journal of Cardiology 133:145-51. https://doi.org/10.1016/j.ijcard.2009.01.073

Yanagisawa D, NF Ibrahim, H Taguchi et al., 2015. Curcumin derivative with the substitution at C-4 position, but not curcumin, is effective against amyloid pathology in APP/PS1 mice. Neurobiology of Aging 36:201-10. https://doi.org/10.1016/j.neurobiolaging.2014.07.041

Ye M, J Zhang, J Zhang et al., 2015. Curcumin promotes apoptosis by activating the p53-miR-192-5p/215-XIAP pathway in non-small cell lung cancer. Cancer Letters 357:196-205. https://doi.org/10.1016/j.canlet.2014.11.028

Yu JJ, LB Pei, Y Zhang et al., 2015. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. Journal of Clinical Psychopharmacology 35:406-10. https://doi.org/10.1097/JCP.0000000000000352

Zhang Q, D Li, Y Liu et al., 2016. Potential anticancer activity of curcumin analogs containing sulfone on human cancer cells. Archives of Biological Sciences 68:125-33. https://doi.org/10.2298/ABS150323134Z

Zhang ZJ, LX Zhao, DL Cao et al., 2012. Curcumin inhibits LPS-induced CCL2 expression via JNK pathway in C6 rat astrocytoma cells. Cellular and Molecular Neurobiology 32:1003-10. https://doi.org/10.1007/s10571-012-9816-4

Zhong W, K Qian, J Xiong et al., 2016. Curcumin alleviates lipopolysaccharide induced sepsis and liver failure by suppression of oxidative stress-related inflammation via PI3K/AKT and NF-kappaB related signaling. Biomedicine & Pharmacotherapy 83:302-13. https://doi.org/10.1016/j.biopha.2016.06.036