The Biological Importance of Curcumin

Merve ARLI [1], Hülya ÇELİK[2*]

[1] *Ağrı İbrahim Çeçen University, Faculty of Pharmacy, Ağrı, Turkey*

mervearli42@gmail.com

[2] *Ağrı İbrahim Çeçen University, Faculty of Pharmacy, Pharmacy Technology Department, Ağrı, Turkey,*
hycelik@agri.edu.tr

Abstract

Turmeric (*Curcuma longa*); In India, China and South East Asia, spices are widely used as aromatic stimulants, food preservatives and coloring materials. Among the people as "castor saffron, turmeric, turmeric, saffron root"; Turmeric as the commonly used name is a yellow-orange colored polyphenolic natural substance derived from *C. longa* rhizomes. In traditional medicine for inflammation and tumors, biliary disorders, anorexia, cough, topical wounds, diabetic wounds, hepatic disorders, rheumatism and sinusitis. It was used as a medicine. In recent years, extensive studies have been conducted to determine the biological activities and pharmacological effects of turmeric and its extracts. Curcumin, which is the main yellow bioactive component of turmeric, is known to have a wide bioactivity such as anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, immunomodulator and antiulcer. Safety assessment studies show that curcumin is well tolerated without toxic effects when used in very high doses. Therefore, curcumin is a substance of high biological importance with the development potential of modern medicine for the treatment of various diseases. For this reason, more scientific studies on curcumin should be done and all the dark sides about this important compound should be illuminated.

Keywords*: Biological activity, Curcumin, Turmeric, C. longa rhizomes, natural*

1. Introduction

Turmeric (*Curcuma longa L.*) belonging to the Zingiberaceae family, is a perennial herbaceous plant with yellow flowers. It grows in the tropical and subtropical regions of Asia, especially in India, China, Indonesia, Jamaica, Peru and Pakistan. The main roots of the plant under the ground are in the form of eggs and pears, and the side roots are in the form of tuber (rhizome). These tubers contain yellow pigments. The plant originating from the tubers of the *Curcuma longa L.* plant is called turmeric (Akbay and Pekcan 2016).

Received:24.05.2020
Accepted:19.06.2020
Published:24.06.2020
[*]*Corresponding author:* Hülya ÇELİK *PhD*
Agri Ibrahim Cecen University, Faculty of Pharmacy, Pharmacy Technology Department, Agrı Turkey
E-mail: hycelik@agri.edu.tr
Cite this article as:M. Arlı and H.Çelik, The Biological Importance of Curcumin, *Eastern Anatolian Journal of Science, Vol. 6, Issue 1, 21-34, 2020.*

Figure 1. *Curcuma longa L.* (*Turmeric*) Plant

History of *Turmeric* (*Curcuma longa*) When looking at ancient scriptures, especially Indian sources, the most important plant encountered is turmeric. Turmeric, also known as "Indian saffron", BC. It was used until 4000. Its name and use is frequently mentioned in the ancient Indian medicine system, Ayurveda. In fact, the use of turmeric; It has spread to many purposes as paint, condiment and medicine. In Sanskrit, turmeric is called "Haridara", a word consisting of two parts. Turmeric has been put into various uses as a flavoring agent with digestive properties as a coloring in India. In fact, no Indian preparation is complete without turmeric as an ingredient. Turmeric is highly respected by Hindus and interestingly given in some temples as "Prasad" (a benevolent material) in powder form. Characa and Susruta, the great ancient Indian physicians who systemized Ayurvedic medicine, recorded various uses of turmeric.

Dioscorides, a Greek doctor in the Roman Army, also mentioned turmeric. European explorers traveling to the Asian continent brought turmeric to the Western world in the fourteenth century. For over 20,000 years, it has been crushed and powdered turmeric rhizome has been widely used in Asian cuisine, medicines, cosmetics, and fabric dyeing. About 40 species of the Curcuma genus are native to India, which indicates their Indian origin. Approximately 70-110 species of species have been reported in Tropical Asia. The species in India, Myanmar and Thailand show the greatest variety. Some species are seen as far away as China, Australia and the South Pacific, while some other popular species are grown in all tropical regions (Nair 2013).

Curcumin was first isolated from turmeric in 1815 and the structure Illuminated in 1910 was defined as diferuloylmethane (curcumin). The most curcumin preparations currently available include approximately 77% diferuloylmethane (curcumin), 18% demethoxycurcumin and 5% bismethoxycurcumin.

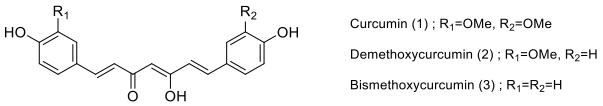

Figure 2. Curcuminoid structures

Turmeric consists of 3-5% Curcuminoid. Curcumin is the most important fraction responsible for the biological activities of turmeric (Çikrikçi et al. 2008). Curcumin is found in the rhizome of *Curcuma longa L.* and other *Curcuma spp* species. Commercially, curcumin is found in the plant at approximately 77%, as well as two other related compounds (bimethoxycurcumin and demethoxycurcumin). These compounds belong to the diarylheptanoid group. These three compounds are

called Curcuminoid. Curcumin appears as a bright orange-yellow crystalline compound. Curcumin is widely used as a coloring and food additive. Curcumin is almost insoluble in water at acidic and neutral pH, but it is soluble in polar and non-polar organic solvents, as well as in highly acidic solvents such as alkali or glacial acetic acid. Curcumin has a melting point of 183 °C. The curcumin molecular formula is $C_{21}H_{20}O_6$, with a molecular weight of 368.38 Dalton. Most studies on curcuminoid compounds have been performed on animals (mice, rats, or dogs), and studies on humans have reported in very few publications. Clinical studies have shown that curcumin is safe for humans even at high doses, but its therapeutic use is very low since its bioavailability is limited. Preclinical studies have reported that curcumin concentrations in plasma and target tissue are very low due to its widespread metabolism (Lestari and Indrayanto 2014; Celik et al.2008).

Uses of Curcumin; Curcumin has been used in traditional Indian and Chinese medicine for centuries, especially as an anti-inflammatory agent. In recent years, several studies of curcumin have been anticarcinogenic, antioxidant, immunomodulatory, antiangiogenic, etc. showed that it has various biological and pharmacological activities. However, preclinical and clinical studies have found that the potentially beneficial effects of curcumin on the prevention and treatment of various diseases are limited to poor pharmacokinetic properties due to its imbalance under physiological conditions that hinder its therapeutic benefit. Curcumin's main structural problem; physiological conditions are the presence of active methylene group and p-diketone fragment, causing curcumin instability under poor absorption and rapid metabolism (Wiggers et al. 2017).

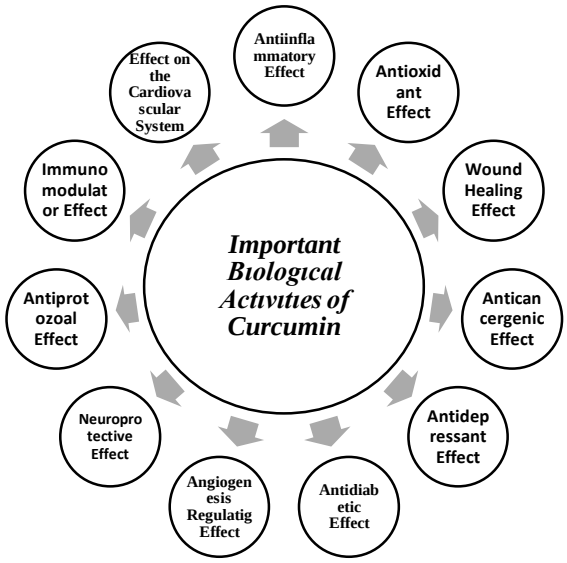

Figure 3. Schematic of the multiple biological activities of turmeric / curcumin

In various scientific studies, curcumin, a polyphenol, has been shown to target multiple signal molecules and also to act at the cellular level, helping to support multiple health benefits. It benefits inflammatory conditions, metabolic syndrome, pain; It has also been shown to assist in the treatment of inflammatory and degenerative eye conditions. It has also been shown to benefit the kidneys. Although there are numerous therapeutic benefits to curcumin supplements, most of these benefits are due to their antioxidant and anti-inflammatory effects. Despite its reported benefits through inflammatory and antioxidant mechanisms, one of the biggest problems in curcumin ingestion by itself is its poor bioavailability, which appears to be mainly due to poor absorption, rapid metabolism and rapid elimination. By addressing these various mechanisms, various substances have been tested to improve the bioavailability of curcumin. Many have been developed to block the metabolic pathway of curcumin to increase its bioavailability. For example, piperine, a known bioavailability enhancer, is the main active

ingredient of black pepper and is associated with a 2000% increase in curcumin bioavailability. Therefore, the problem of poor bioavailability appears to be solved by adding agents such as piperine that increase bioavailability and creating a curcumin complex (Hewlings and Kalman 2017).

Synthesis of synthetic analogues can be shown as one of the studies to increase the biological activity of curcumin. In addition to synthetic analogues, other strategies have been considered to increase the biological activity of curcumin. These strategies include adjuvants, nanoparticles, liposomes, micelles and phospholipid complexes. The adjuvants were selected on the basis of their ability to prevent the rapid metabolism of curcumin by interfering with enzymes that catalyze curcumin metabolism. All other formulations mentioned are primarily designed to increase the absorption of curcumin into tissues. Nanoparticles can provide greater penetration into membrane barriers due to their small size. Besides their size, their modification potentials targeting specific organs make them excellent drug carriers. Liposomes, micelles and phospholipid complexes can reduce the hydrophobicity of curcumin; these carriers can also interact with the membrane components to increase the permeability of the membrane barriers. Recently, it has been reported that the water solubility of curcumin can be 12 times with the use of heat (Kurien et al 2007).

Curcumin is recognized and used worldwide for many potential health benefits. For example, turmeric containing curcumin in India has been used in curries, served as tea in Japan, used in cosmetics in Thailand, used as a colorant in China, served in drinks in Korea, used as an antiseptic in Malaysia, a in Pakistan used as an anti-inflammatory agent and in the United States in mustard sauce, cheese, butter and chips; It is used in addition to capsules and powder forms as a preservative and coloring agent. Curcumin capsule, tablet, ointment, energy drink, soap, cosmetics, etc. various forms are available. Curcuminoids have been approved by the U.S. Food and Drug Administration (FDA) as GRAS (Generally Recognized as Safe), and good tolerability and safety profiles have been demonstrated by clinical studies even at doses from 4000 to 8000 mg / dose (Hewlings and Kalman 2017).

In this research study, curcumin, which is the main active ingredient of turmeric, which has a wide range of uses, is aimed to illuminate a few of its important biological activities.

Figure 4. Turmeric (Curcuma longa)

Anticancergenic Activity

Curcumin has attracted attention in cancer researches in recent years due to its cancer suppressor feature. It has been shown in many cancer types as an anticancer effective agent in studies that suppress tumor formation. Curcumin obtained from turmeric; It has been used for centuries to treat various inflammatory diseases. The turmeric; cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and reduction of receptors in antiapoptotic genes), proliferation (HER-2, EGFR, AP-1), survival (PI3K / AKT pathway), spread (MMP-9 and adhesion molecules), new blood vessel network formation (VEGF), metastasis (CXCR-4), inflammation (NF-

KB, TNF, IL-6, IL-1, COX-2, VE 5-LOX) and their multiple cells signal is thought to act by interfering on the path. Curcumin has been reported to suppress tumor formation in leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous (flat) carcinoma, lung cancer, melanoma and neurological cancers (Anand et al. 2008). Although traditional herbal medicines are thought to be safe, it is not known exactly what their active principles are and how they mediate cancer. Phenolic compounds; It exhibits antioxidant and anticancer activity thanks to its free radical scavenger properties. Curcumin has excellent antioxidant activity due to its phenolic and enolic functional groups (Sharma et al. 2005). Studies have confirmed that aromatic rings with curcumin and their analogs show cytostatic activity. Curcumin has antineoplastic activity, low molecular weight and no toxicity. makes it the ideal precursor molecule in the development of potential chemotherapeutic drugs. Based on the chemical structure of curcumin, various analogues are synthesized and their effects are tested (Youssef et al 2007; Tomeh et al.2019; Vallianou et al. 2015).

Anti-inflammatory and Antioxidant Activity

Numerous studies have been conducted on curcumin, especially in respiratory diseases. Curcumin is used in Eastern medicine for the treatment of various chronic inflammatory diseases, including respiratory diseases. Curcumin has been shown to reduce inducible nitric oxide synthase activity in aspiration induced airway damage in rats. Sharma (1976) reported that the antioxidant property of curcumin is due to its phenolic structure and prevents apoptosis by restoring growth-inhibited cells. Turmeric increases the duration of protection by preventing the formation of peroxide in foods. Turmeric has been reported to be more effective than vitamin E in preventing lipid oxidation. It has been determined that the components isolated from Curcuma longa have a strong antioxidant effect and are very important on lipid oxidation (Jayaprakasha et al. 2005; Wright 2002).

Curcumin also inhibits neural activation, mixed lymphatic reaction, and platelet development by eliminating mitogens that cause rapid growth of mononuclear blood cells (Huang 1992). It also partially inhibits the protein kinase enzyme (Liu 1993). Oxidative stress is known to play an important role in the pathogenesis of many diseases, including myocardial ischemia, brain ischemia-reperfusion injury, bleeding, shock, nervous cell damage, and cancer. Curcumin has proven anti-inflammatory and antioxidant properties. Curcumin has been reported to remove different types of reactive oxygen, including hydroxyl radicals (Reddy and Lokesh 1994) and nitrogen dioxide radicals (Unnikrishnan and Rao 1995, Sreejayan and Rao 1997). Khanna (2009) stated that the antioxidant capacity of curcuminoids is equivalent to ascorbic acid. Curcumin is a powerful hydroxyl radical scavenger as well as capturing superoxide radicals. It protects DNA from oxidative damage due to its ability to retain free radicals (Pandya et al 2000). When curcumin is taken orally, it turns into tetrahydrokurumin by hydrogenation in the intestines. It is absorbed from the intestines, distributed into the blood and thus tissues, and is excreted in bile. Davis et al. (2007) showed that curcumin supplementation reduced muscle damage caused by excentric exercise in rats (Boz 2013; Aggarwal 2009).

Local application of turmeric is used in skin diseases, insect bites and chickenpox in India. It has been used as an alternative medical support for wound

healing for many years. Wound contraction is faster in myofibroblasts treated with curcumin. As a result of curcumin treatment, fibronectin and collagen expression increases. In addition, the formation of granulation tissue, neovascularization re-epithelialization increases in mouse wound models formed with diabetic and hydrocortisone. Curcumin has been shown to reduce hydrogen peroxide-induced damage in yellow keratinocytes and fibroblasts. Jagetia looked at wound healing in Swedish albino mice by willing the body half in multiple fractionated doses; evaluated dose-dependent wound contractions and wound healing in animals examined on days 4, 8, and 12 after radiation exposure. It has been shown that curcumin administered before treatment significantly reduces wound contraction and average wound healing time. With curcumin treatment, collagen, hexosamine, DNA, nitrate, and nitrite synthesis increased before the radiation, and collagen accumulation, fibroblast and vascular densities also increased. In the acute ulcer model created in mice, it also shows antiulcer effect by decreasing lipid peroxidation and protein oxidation. Epithelial cell damage in the gastic lumen is reversible by providing reepithelialization with curcumin (Uzer 2007).

As a result, curcumin has been found to have powerful modulating effects on wound healing. Studies have shown that curcumin does this by acting in the inflammatory, proliferative and remodeling stages of the wound healing process, and by doing so it reduces the time required for wound healing. Unfortunately, curcumin is limited by its low bioavailability, rapid metabolism, poor solubility and light sensitivity. In order to minimize these effects and to use curcumin to its maximum capacity, new formulations such as nanoparticles should be investigated (Akbik et al. 2014; Jurenka 2009).

Angiogenesis Activity

Angiogenesis is a physiological process characterized by the formation of new vascular capillary canals. These steps extend from embryonic development, production processes, wound healing to bone healing. On the other hand, there are many pathological conditions related to uncontrolled angiogenesis. Tumor growth, Rheumatoid Arthritis, Diabetic Retinopathy and hemangiomas can be counted. In the last 30 years, intensive studies have been conducted on the growth of primary tumor and its role in angiogenesis in distant metastases. Curcumin has been beneficial in many models as a regulator of uncontrolled angiogenesis. In laboratory conditions, angiogenic differentiation with curcumin in human umbilical vein endothelial cells, mouse oral mucosa cells and chicken chorioallantoic membrane cells was inhibited. In a different study, corneal neovascularization was inhibited in the mouse cornea with a basic fibroblast growth factor (bFGF) stimulus. This effect can be explained by the fact that curcumin analogs reduce over-expression of genes associated with angiogenesis. Curcumin and its analogs inhibit metalloproteinases and reduce angiogenesis in tumor tissues (Uzer 2007; Wang and Chen 2019).

Antineuroprotective Activity

Curcumin (*Curcuma longa*), a biologically active component of turmeric, is used as a curry spice and herbal remedy for the treatment of inflammatory conditions, cancer, AIDS and other diseases. Epicchemical studies in India, where turmeric is routinely used, show that the incidence of AD between the ages of 70 and 79 is 4.4 times less than in the USA. The researchers used transgenic mouse APPSw to investigate curcumin therapeutic effect. The results

show that low-dose curcumin significantly suppresses inflammatory cytokine IL-1 and astrocytic marker GFAP, reduces oxidative damage and plaque burden, and reduces the amount of insoluble amyloid. Compared to other antioxidant drugs such as NSAID or ibuprofen, curcumin has less side effects. Evidence shows that metals are concentrated in the AD brain and curcumin is a chelating agent that can bind iron and copper (not zinc) onto beta amyloid, which could potentially contribute to amyloid reduction. In vivo, curcumin can protect cells from beta amyloid attack and subsequently damage from oxidative stress in the antioxidant pathway.

Curcumin significantly improved the memory ability of AD mice in step test testing, as indicated by reduced number of step-by-step errors and extended step-by-step latency. Curcumin also relieved neuropathological changes in the hippocampus and inhibited apoptosis with an increase in Bcl-2 level, but Bax activity did not change. Curcumin increased cell viability in the presence of ALCL. The rate of apoptosis decreased significantly in the curcumin group, when measured by flow cytometric analysis. Curcumin preserved cells by increasing the Bcl-2 level, but the Bax level has not changed. In this study, curcumin was found to increase the memory ability of AD mice (Pan et al. 2008; Amalraj et al.2017)

Antidepressant Activity

Several traditional Chinese herbal medicines such as Xiaoyao-san and Jieyu-wan, which were prescribed by the famous Chinese folk doctor Zhong-jing Zhang thousands of years ago; It has been used in the treatment of mental stress, hypochondriac intense pain, hysteria and manic. Various findings in recent preclinical studies have supported the therapeutic value of herbal medicines in a clinical setting. In laboratory studies of animals, Xiaoyao-san has been shown to have antidepressive-like effects using tail suspension and forced swimming tests. In the study of Ying et al., The effects of curcumin on depressive-like behaviors in mice were analyzed using two animal depression models. The results showed that curcumin treatment at 5 and 10 mg / kg (po) significantly reduced inactivity. In both tail suspension and forced swimming tests. These doses that affect the inactive response did not affect locomotor activity. In addition, neurochemical analysis showed that curcumin produced a marked increase in serotonin and noradrenaline levels at 10 mg / kg in both the frontal cortex and hippocampus. Dopamine levels also increased in the frontal cortex and striatum. In addition, curcumin has been found to inhibit monoaminoxidase activity in the mouse brain. These findings suggest that the antidepressant-like effects of curcumin may include central monoaminergic neurotransmitter systems. Therefore, the results of the study show that curcumin has antidepressant properties in behavioral hopelessness tests and the effects may be related to monoaminergic systems. These studies may contribute to understanding the mechanisms of curcumin antidepressant effects. The modified amine theory suggests that an acute increase in monoamine levels in synapse can only be an early step in a potentially complex sequence of events that ultimately leads to antidepressant activity. Given that chronic antidepressant effects are frequently seen after chronic treatment, the long-term effects of curcumin should be evaluated and further studies should focus on receptors and signal transduction to explain the detailed mechanisms of the curcumin antidepressant effect (Ying et al. 2005; Kulkarni 2009).

Antiprotozoal Activity

The antiprotozoal activities of curcumin have been extensively studied in the past decade. Turmeric (1% raw extract), as well as its functional and medicinal ingredient, curcumin (0.05%), seems to be effective in reducing upper and middle-small bowel infections caused by Eimeria acervulina and E. maxima. It is useful in E. tenella infections. However, in vitro incubation of E. tenella sporozoites with curcumin showed significant effects on sporozoite morphology and viability, leading to reduced invasion of MDBK cells. The curcumin alcohol extract has been found to have antiprotozoal activity. Against Entamoeba histolytica. Curcumin antiprotozoal activities have also been reported for Plasmodium, Leishmania, Trypanosoma and Giardia lamblia both in vitro and in vivo. Curcumin reduced parasitemia by 80% to 90% in mice infected with Plasmodium berghei. In another study, curcumin was found to be effective against Cryptosporidium parvum in cell culture. *C.parvum* has been found to be more sensitive to curcumin than Plasmodium, Giardia and Leishmania. Synergistic antiprotozoal effects have been shown when curcumin is administered in combination with other drugs. For example, the combination of artemicin and curcumin exhibited additional activity in the culture killing of Plasmodium falciparum and allowed survival of mice infected with P. berghei. Drug resistance of plasmodium strains is a major threat to malaria control. However, chloroquine-resistant P. falciparum and artemisinin-resistant Plasmodium chabaudi were found susceptible to curcumin in cultures and mice, respectively. These are promising data that can open alternative options for malaria control, especially where drug resistance has become a relevant issue.

Curcumin's antiparasitic activities are obtained by effects on the transcription of genes. Recent studies have shown that histone acetylation plays an important role in eukaryotic gene expression and antiparasitic therapy. The balance between acetylation and deacetylation of histones is correctly maintained by histone acetyltransferase (HAT) and histone deacetylase balance. Curcumin induces histone hypoacetylation mainly in vivo through HAT inhibition and simultaneous effects of curcumin with ROS production, it also contributes to the inhibition of HAT activity. Curcumin inhibits intracellular adhesion molecules that contribute to the sequestration and formation of Toxoplasma and has been associated with a glutathione transferase (PfGST) chloroquine resistance isolated from Plasmodium P. falciparum. Curcumin is a powerful PfGST inhibitor that can open alternative perspectives for the management of drug resistance in malaria. It inhibits metalloproteinase activity comparable to classical matrix metalloproteinase inhibitors such as curcumin, EDTA, EGTA, phenanthroline and also trypanosoma brucei infection, such as tetracycline. Survivin's curcumin-mediated downregulation induces apoptosis in tumor cells and can likewise increase the apoptosis of C. parvum. Infected cells. Curcumin can effectively regulate NF-kB, thereby inhibiting IkappaBalpha kinase and reducing IkappaBalpha phosphorylation, leading to cell cycle arrest, apoptosis and proliferation of parasitically infected cells. Inhibition of thioredoxin reductase by curcumin may reduce parasite proliferation, which is attractive for control strategies (Parasuraman 2017; Rasmussen et al.2000)

Antidiabetes Activity

Curcumin is used in ayurveda and traditional Chinese medicine for the treatment of diabetes. It is thought to be a potential treatment for diabetes and its complications as it is a relatively safe and inexpensive

drug that reduces glycemia and hyperlipidemia in diabetes models (Zhang et al 2013). In a study, the effects of curcumin with antioxidant and anti-inflammatory properties on diabetic oxidative stress and inflammation in the retina of mice were investigated. One group of diabetic mice induced with streptozotokin was given a powder diet supplemented with 0.05 curcumin (w/w) and a diet without curcumin was applied to the other group. Mice were sacrificed 6 weeks after induction of diabetes. The retina has been used to identify oxidative stress and proinflammatory signs. At the end of the study; antioxidant capacity and intracellular antioxidant levels, GSH levels decreased about 30-35%. Application of curcumin prevented a decrease in antioxidant capacity from diabetes. Curcumin effects were achieved without correction of severe hyperglycemia. In this case, curcumin has been suggested to have beneficial effects on metabolic abnormalities (Kowluru and Kanvar 2007).

In a study on the anti-inflammatory, antioxidant, hypoglycemic and lipid-lowering effects of turmeric extract; live subjects induced by high fat diet were divided into two groups and extract was given to one of these groups at determined doses. In the extract group, turmeric showed a strong inhibitory effect against the oxidation of LDL (low density lipoprotein) and glycation caused by fructose due to the high radical scavenging effect caused by the antioxidant activity. As a result, turmeric extract has been declared to prevent glycation due to its strong antioxidant activity, decreases LDL (low density lipoprotein) and thus reduces the risk of atherosclerosis (vascular stiffness) (Kubra et al. 2010).

In a study on the effect of Curcuma longa extract on plasma glucose and insulin; Research has been conducted on 14 healthy volunteers (7 men, 7 women). Orally 6 g Curcuma longa extract was given on certain days and insulin levels were checked at certain time intervals. It was observed that satiety insulin levels increased in these groups of people given Curcuma longa extract. As a result, it has been scientifically explained that *C. Longa* extract has positive effects on insulin release in humans (Wickenberg et al. 2010).

Anticardiovascular Activity

The protective effects of turmeric on the cardiovascular system include lowering cholesterol and triglyceride levels, lowering the sensitivity of low-density lipoprotein (LDL) to lipid peroxidation and inhibiting platelet aggregation. These effects are noted even with a low dose of turmeric. In a study of 18 atherosclerotic rabbits given a low dose of turmeric extract (1.6-3.2 mg / kg body weight per day), LDL's sensitivity to lipid peroxidation in addition to low plasma cholesterol and triglyceride levels has been shown to decrease. The higher dose did not reduce the lipid peroxidation of LDL, but to a lesser extent than the low dose, the level of cholesterol and triglycerides decreased. The effect of turmeric extract on cholesterol levels may be due to decreased cholesterol intake in the intestines and increased conversion of cholesterol to bile acids in the liver. Inhibition of platelet aggregation by C. longa components is thought to be by enhancing prostacyclin synthesis and inhibition of thromboxane synthesis (Akram et al. 2010; Gupta et al. 2012).

Anti-AIDS Activity

There are several reports showing that curcumin may have potential against AIDS. These effects of curcumin are mediated by inhibition of HIV long terminal repeat and HIV protease and inhibition of human immunodeficiency virus (HIV) replication, inhibit HIV-1 integration, p300 / CREB binding

protein specific acetyltransferase and chromatin dependent of histone / non histone proteins and histone acetyltransferase. Suppresses the acetylation of its transcription. For this reason, curcumin also has great potential against AIDS (Jagetia and Aggarwal 2007; Mazumdar et al. 1995).

Antigastrointestinal Activity

Curcuma longa components are known to exert various protective effects on the gastrointestinal tract. Sodium curcuminate has been shown to inhibit intestinal spasm and turmeric component p tolmethylcarbinol, increased gastrin, secretin, bicarbonate and pancreatic enzyme secretion. Turmeric has also been shown to inhibit the formation of stress, alcohol, indomethacin, pyloric ligation and ulcer-induced ulcer, and significantly increase gastric wall mucus in rats exposed to these gastrointestinal insults (Akram et al. 2010; Kwiecien et al. 2019).

Antiimmunomodulator Activity

The immune system has evolved to protect the host from microbial infection; However, a disruption in the immune system often results in infection, cancer, and autoimmune diseases. Multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, myocarditis, thyroiditis, uveitis, systemic lupus erythromatosis, and myasthenia are organ-specific autoimmune diseases that affect more than 5% of the population worldwide. Although its etiology is not known but still requires a treatment, the use of herbal and dietary supplements is increasing in patients with autoimmune diseases, as they are mainly effective, inexpensive and relatively safe. Recent studies have shown that curcumin improves multiple sclerosis, rheumatoid arthritis, psoriasis and inflammatory bowel disease in human or animal models. Curcumin inhibits these autoimmune diseases by regulating inflammatory cytokines in immune cells such as IL-1β, IL-6, IL-12, TNF-a and IFN-y and associated JAK-STAT, AP-1 and NF-kB signaling pathways. Although the beneficial effects of nutraceuticals have traditionally been achieved with low levels of dietary consumption for a long time, the use of purified active compounds such as curcumin for therapeutic purposes requires extreme caution (Bright 2007).

According to many studies, curcumin increases immunity. Curcumin can also help the body fight cancer if some cells escape apoptosis. The researchers found that when they looked at the lining of the intestine after curcumin intake, the number of CD4 + T helper and B-type immune cells was higher. In addition to this localized immune stimulation, curcumin also increases immunity in general. Researchers in India have documented increased antibodies and greater immune action in mice given curcumin (Akram et al. 2010; Srivastava et al. 2011).

Antiviral Activity

In the study of Joe et al. Olarak In vitro, curcumin (0.32 mg / ml) partially inhibited the activity of the human simplex virus-2 (Bourne et al. 1999). Curcumin provided significant protection in a mouse model of the intravaginal human simplex virus-2 threat (Bourne et al. 1999). Curcumin is also highly effective in inhibiting Type I Human Immunodeficiency Virus (HIV) long terminal repeat directed gene expression and viral replication (Jiang et al. 1996; Li et al. 1993). Curcumin inhibited the production of p24 antigen in acute or chronically infected cells with HIV-1 (Li et al. 1993). However, curcumin was unable to inhibit HIV-

1 proliferation in acute infected MT-4 cells (Artico et al. 1998). However, curcumin specifically inhibited enzymatic reactions associated with HIV-1 integrase, but other viral (HIV-1 reverse transcriptase) and cellular (RNA polymerase II) nucleic acid processing enzymes (Artico et al., 1998; Burke et al., 1995). Mazumder et al. (1997) synthesized and tested curcumin analogs to examine the structure-activity relationships and mechanism of action of this family of compounds in more detail. The two curcumin analogues, dichopeoylmethane and rosmarinic acid inhibited the integrase activity with IC50 values below 10 μM. The two curcumin analogues showed lysine 136 (required for viral DNA binding) and equivalent potencies in wild-type integrase. Curcumin binding site and substrate binding site may not overlap (Mazumder et al. 1997). Combination of a curcumin analog with the recently described integrase inhibitor NSC 158393 resulted in synergistic or reflective integrase inhibition of drug binding sites that may not match. They also determined that these analogs could prevent the enzyme from binding to viral DNA, but this inhibition was independent of the divalent metal ion. In addition, kinetic studies of these analogs suggest that they bind slowly to the enzyme (Mazumder et al. 1997; Joe et al 2004).

Use in Ischemia

Neuronal energy metabolism is dependent on oxygen and glucose and cannot cope with hypoxic or hypoglycemic periods. A decrease in oxygen or glucose concentrations in the brain inevitably leads to loss of neuronal function. Ischemia is caused by a deficiency in blood flow to the brain or areas of the brain, as in stroke. The results of ischemia are an increase in intracellular Ca2 + levels through excessive mitochondrial production of reactive oxygen species, activation of the NMDA receptor, stimulation of astrocytes, and neuronal death. Evidence from animal models shows that curcumin can protect against ischemic damage. In addition to keeping the injured area in the brain, curcumin can reduce oxidative damage and mitochondrial dysfunction, as well as inhibit neuronal apoptosis and microglial activation. During and after ischemia, other inflammatory agents are produced, such as leukotriene and cytokine, which facilitate infiltration of leukocytes. Proteolytic enzymes from recruited leukocytes disperse the blood-brain barrier, resulting in edema in damaged brain tissue. Application of curcumin to laboratory rodents can prevent edema and maintain the integrity of the blood-brain barrier. Their significant improvement in cognitive performance is now observed in curcumin-treated animals as compared to untreated ischemic controls. Interestingly, curcumin can provide significant protection from the harmful effects of ischemia, regardless of the route of administration (intraperitoneal injection, gavage or dietary supplement). Despite the large available data on the anti-ischemic effects of curcumin in animal models, studies in humans are scarce. In fact, a possible therapeutic application of curcumin in cases of stroke and ischemia is controversial. On the one hand, curcumin and its synthetic derivatives (CNB - 001) are considered potential neuroprotectants based on epidemiological observations and preclinical data. However, in order to achieve levels comparable to those used in animal models, high concentrations of curcumin will be required daily (Esatbeyoğlu et al. 2012; Bavarsad et al. 2018).

2. Discussion

Turmeric (curcumin) is known to give positive results in the treatment of many diseases such as

neurological diseases, indigestion, urinary system infections, liver diseases, rheumatoid arthritis, respiratory system diseases, obesity, diabetes, cancer. Curcumin is the most important active ingredient responsible for the biological activities of turmeric. Curcumin has been used for centuries due to its non-toxic and potential therapeutic effects. As a result of the studies, the tolerability and safety of this polyphenol (curcumin) at doses not exceeding 8 mg per day revealed that it is non-toxic. In addition to the use of sweeteners and colorants in nutrition, curcumin antioxidant, antimutagenic, antidiabetic, antibacterial, antiviral, anti-inflammatory, antinociceptive anti-inflammatory, anticancer, antioxidant, anti-protozoal, anti-microbial, antimalarial, antiinflammatory, antiproliferative, anti-inflammatory, anti-inflammatory, antiproliferative, antiproliferative, antiproliferative, antiproliferative, anti-inflammatory It has. With its reliability, low cost and proven efficacy, turmeric is a promising natural medicine for diseases. It is seen that more comprehensive studies are needed since there are not enough studies in terms of drug interactions. Turmeric must be present in our daily diet.

Acknowledgement

This study was prepared from Meve Arlı's Research Project Thesis.

References

AGGARWAL, B.B, HARIKUMAR, K.B (2009). Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol 41: 40-59.

AKBİK, D. GHADİRİ, M.CHRZANOWSKİ, W. ROHANİZADEH, R. (2014). Curcumin as a Wound Healing Agent. *Life Sciences, 116* (1), 1-7.

AKRAM, M. SHAHAB-UDDİN, A. A. USMANGHANİ, K. HANNAN, A. MOHİUDDİN, E. ASİF, M. (2010). Curcuma longa and curcumin: a review article. *Rom J Biol Plant Biol, 55*, 65–70.

AMALRAJ A. PİUS, A. GOPİ, S. GOPİ, S. (2017), Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – a review J. Tradit. Complement. Med. 7 (2) pp. 205-233.

ANAND, P. THOMAS, S. KUNNUMAKKARA, A., SUNDARAM, C. HARİKUMAR, K. B., SUNG, B. THARAKAN, S. T. MİSRA, K. PRİYADARSİNİ, I. K. RAJASEKHARAN, K. N. AGGARWAL, B. B. (2008). Biological activities of curcumin and its analogues(congeners) made by man and mother nature. *Biochem Pharm, 7*(6), 1590–611.

ARTİCO, M. Dİ SANTO, R. COSTİ, R. NOVELLİNO , E. GRECO, G. MASSA, S. TRAMONTONO, E. MARONGİU, M.E. DE MONTİS, A. LA COLLA, P. (1998). Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of HIV-I intergrase. *Journal of Medicinal Chemistry, 41*, 3948-3960.

BAVARSAD, K. BARRETO, G.E, HADJZADEH, M.A, SAHEBKAR, A (2018). Protective effects of curcumin against ischemia-reperfusion injury in the nervous system. Mol Neurobiol.

BOURNE, K. Z. BOURNE, N. REİSİNG, S.F. STANBERRY, L.R. (1999). Plant products as topical microbicide candidates: assessment of in vitro and in vivo activity against herpes simplex virus type 2. *Antivir. Res., 42*, 219-226.

BOZ, İ. (2013). *Kurkumin Takviyesinin Sıçanlarda Ekzantrik Egzersizle Oluşan Kas Hasarı Üzerine Etkisi.* Yüksek Lisans Tezi, T.C. Selçuk Üniversitesi Sağlık Bilimleri Enstitüsü, Konya.

BRİGHT, J. J. (2007). Curcumin and autoimmune disease. *Adv Exp Med Biol, 595*, 425–451.

BURKE, J.R. T. R., FESEN, M. R. MAZUMDER, A. WANG, J. CAROTHERS, A. M. GRUNBERGER, D. DRİSCOLL, J. KOHN, K., POMMİER, Y. (1995). Hydroxylated aromatic inhibitors of HIV-1 integrase. *J. Med. Chem., 38* , 4171-4178.

CELIK, H. AYDIN, T. SOLAK, K. KHALID, S. F AROOQI A. A. (2018), Curcumin on the "flying carpets" to modulate different signal

transduction cascades in cancers: Next-generation approach to bridge translational gaps. J. Cell. Biochem. 119, pp. 4293-4303.

DAVİS, J. M. MURPHY, E. A. CARMİCHAEL, M. D. ZİELİNSKİ, M. R. GROSCHWİTZ, C. M. BROWN, A. S. GANGEMİ, J. D. GHAFFAR, A. MAYER, E. P. (2007). Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage. *Am J Physiol Regul Integr Comp Physiol., 292*(6), R2168-73.

DELIKANLI AKBAY, G. PEKCAN, A. G. (2016). Zerdeçal: Beslenme ve Sağlık Yönünden Değerlendirilmesi. *Beslenme ve Diyet Dergisi, 44*(1), 68-72.

ESATBEYOĞLU, T. HUEBBE, P. ERNST, I. M. CHİN, D., WAGNER, A. E. RİMBACH, G. (2012). Curcumin-from molecule to biological function. *Angew Chem Int Ed Engl., 51*(22), 5308-32.

GUPTA S.C, PATCHVA S, KOH W, AND AGGARWAL B.B. (2012), Discovery of curcumin a component of golden spice and its miraculous biological activities. Clin. Exp. Pharmacol. Physiol. 39:283–299.

HEWLİNGS, S. J. KALMAN, D. S. (2017). Curcumin: A Review of Its' Effects on Human Health. *Foods, 6*(10), 92.

HUANG, H. C. JAN, T. R. YEH, S. F. (1992). Inhibitory effect of curcumin, an anti-inflammatory agent, on vascular smooth muscle cell proliferation. *European Journal of Pharmacology, 221*(2-3), 381-384.

JAGETİA, G. C. AGGARWAL, B. B. (2007). "Spicing up" of the immune system by curcumin. *J Clin Immunol, 27*, 19-35.

JAYAPRAKASHA, G. K. RAO, L. J. SAKARİAH, K. K. (2005). Chemistry and biological activities of C. longa. *Trends Food Sci. Technol., 16*, 533–548.

JİANG, M. C. YANG-YEN, H. F. LİN, J. K. YEN, J. J. (1996). Differential regulation of p53, c-myc, Bcl-2 and Bax protein expression during apoptosis induced by widely divergent stimuli in human hepatoblastoma cells. *Oncogene, 13*, 609-616.

JOE, B. VİJAYKUMAR, M. LOKESH, B. R. (2004). Biological Properties of Curcumin-Cellular and Molecular Mechanisms of Action. *Critical Reviews in Food Science and Nutrition, 44*(2), 97-111.

JURENKA, J. S (2009). Anti-inflammatory Properties of Curcumin, a Major Constituent of Curcuma longa: A Review of Preclinical and Clinical Research. Altern Med Rev 14: 141-153.

KHANNA, S. PARK, H. A., SEN, C. K., GOLAKOTİ, T., SENGUPTA, K., VENKATESWARLU, S., & ROY, S. (2009). Neuroprotective and antiinflammatory properties of a novel demethylated curcuminoid. *Antioxid Redox Signal, 11*(3), 449-68.

KOWLURU, R. A. KANWAR, M. (2007). Effects of curcumin on retinal oxidative stress and inflammation in diabetes. *Nutrition & Metabolism (London), 4*(2007), 8.

KULKARNI, S.K, DHIR, A. AKULA, K.K (2009). Potentials of Curcumin as an Antidepressant. Scientific World Journal 9: 1233-1241.

KURİEN, B. T. SİNGH, A. MATSUMOTO, H. SCOFİELD, R. H. (2007). Improving the solubility and pharmacological efficacy of curcumin by heat treatment. *Assay Drug Dev. Technol., 5*, 567–576.

KWIECIEN, S. MAGIEROWSKI, M. MAJKA, J. PTAKBELOWSKA, A. WOJCIK, D. SLI WOWSKI, Z. BRZOZOWSKI, T. (2019). Curcumin: A potent protectant against esophageal and gastric disorders,International Journal of Molecular Sciences, 20 (6).

LESTARİ, M. L. INDRAYANTO, G. (2014). Chapter Three- Curcumin. *Profiles of Drug Substances, Excipients and Related Methodology, 39*, 113-204.

Lİ, C. J. ZHANG, L. J. DEZUBE, B. J. CRUMPACKER, C. S. PARDEE, A. B. (1993). Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proc Natl Acad Sci USA, 90*(5), 1839–1842.

LİU, J. Y. LİN, S. J. LİN, J. K. (1993). Inhibitory effects of curcumin on protein kinase C activity induced by 12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells. *Carcinogenesis, 14*(5), 857-861.

MAZUMDER, A. NEAMATİ, N. SUNDER, S. SCHULZ, J., PERTZ, H. EİCH, E. POMMİER, Y. (1997). Curcumin analogs with altered potencies against HIV-1 integrase as probes for biochemical mechanisms of drug action. *J. Med. Chem., 40*, 3057–3063.

MAZUMDAR, A. RAGHAVAN, K. WEINSTEIN, J. KOHN, K. W. AND POMMER, Y. (1995). Inhibition of human immunodeficiency virus type-1 integrase by curcumin. Biochem. Pharmacol. 49, 1165–1170.

MOZİOĞLU, E. YILMAZ, H. ÇIKRIKÇI, S. (2008). Biological Activity of Curcuminoids Isolated from Curcuma longa. *Records Of Natural Products, 2*(1), 19-24.

NAGARAJAN, S. KUBRA, I. R. RAO, L. J. (2010). Separation of Curcuminoids Enriched Fraction from Spent Turmeric Oleoresin and Its Antioxidant Potential. *J. Food Science, 75*, 158-162.

NAİR, K. P. (2013). The Agronomy and Economy of Turmeric and Ginger. *Elsevier, Oxford*.

PAN, R. QİU, S., LU, D. DONG, J. (2008). Curcumin improves learning and memory ability and its neuroprotective mechanism in mice. *Chin Med, 121*(9), 832-839.

PANDYA, U. SAİNİ, M. K., JİN, G. F. AWASTHİ, S. GODLEY, B. F. AWASTHİ, Y. C. (2000). Dietary curcumin prevents ocular toxicity of naphthalene in rats. *Toxicology Letters, 115*(3), 195-204.

PARASURAMAN, S. ZHEN, K. M. BANİK, U. CHRİSTAPHER, P. V. (2017). Ameliorative Effect of Curcumin on Olanzapine-induced Obesity in Sprague-Dawley Rats. *Pharmacognosy Research, 9*(3), 247-252.

RASMUSSEN, H. B., CHRISTENSEN, S. B., KUIST, L. P. AND KARAZMI, A. (2000), A simple and effective separation of the curcumins, the antiprotozoal constituents of Curcuma longa. Planta Med., 66, 396–398.

REDDY, A. C., LOKESH, B. R. (1994). Studies on the inhibitory effects of curcumin and eugenol on the formation of reactive oxygen species and the oxidation of ferrous iron. *Molecular and Cellular Biochemistry, 137*(1), 1-8.

SHARMA , R. A. GESCHER, A. J. STEWARD, W. P. (2005). Curcumin: the story so far. *Eur J Cancer, 41*, 1955-68.

SHARMA, O. P. (1976). Antioxidant activity of curcumin and related compounds. *Biochemical Pharmacology, 25*(15), 1811-1812.

SRIVASTAVA R, SINGH S, DUBEY S, MISRA K, KHAR A (2011). Immunomodulatory and therapeutic activity of curcumin. Int Immunopharmacol. 11: 331-341.

SREEJAYAN, RAO, M. N.A. (1997). Nitric oxide scavenging by curcuminoids. *Journal of Pharmacy and Pharmacology, 49*(1), 105-107.

TOMEH M.A, HADIANAMREI R, ZHAO X (2019) A review of curcumin and its derivatives as anticancer agents. Int J Mol Sci 20(5):pii: E1033.

UNNİKRİSHNAN, M. K., RAO, M. N. (1995). Curcumin inhibits nitrogen dioxide induced oxidation of hemoglobin. *Molecular and Cellular Biochemistry, 146*(1), 35-37.

UZER, N. (2007). *Sıçanlarda Deri Fleplerinin Yaşayabilirliğinde Curcumin Kullanımının Etkilerinin Araştırılması.* Uzmanlık Tezi, T.C Sağlık Bakanlığı Şişli Etfal Eğitim ve Araştırma Hastanesi Plastik, Rekonstruktif ve Estetik Cerrahi Kliniği , İstanbul.

VALLIANOU N.G, EVANGELOPOULOS A, SCHIZAS N, KAZAZIS C (2015). Potential anticancer properties and mechanisms of action of curcumin. Anticancer Res 35(2):645–651.

WANG T.Y. CHEN J.X (2019). Effects of curcumin on vessel formation insight into the pro- and antiangiogenesis of curcumin. Evid Based Complement Alternat Med 2019: 1390795.

WİCKENBERG, J. INGEMANSSON, S. L. HLEBOWİCZ, J. (2010). Effects of Curcuma longa (turmeric) on postprandial plasma glucose and insulin in healthy subjects. *Nutrition Journal, 9:43*.

WİGGERS, H. ZAİONCZ, S. CHELESKİ, J. MAİNARDES, R. KHALİL, N. (2017). Curcumin, a multitarget phytochemical. *Studies in Natural Products Chemistry, 53*, 243-276.

WRIGHT, J. S (2002). Predicting the antioxidant activity of curcumin and curcuminoids. *J Mol Struct (Theochem)* **591**, 207–217.

YİNG, X. BAO-SHAN, K. HAİ-YAN, Y. YAN-HUA, L. XİNG, M. YONG-HE, Z. XUE-JUN, L. (2005). Antidepressant effects of curcumin in the forced swim test and olfactory bulbectomy models of depression in rats. *Pharmacology, Biochemistry and Behavior, 82*(1), 200-206.

YOUSSEF, D. NİCHOLS, C. E. CAMERON, T. S. BALZARİNİ, J. CLERCQ, E. D. JHA, A. (2007). Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues. *Bioorganic & Medicinal Chemistry Letters, 17*(20), 5624-5629.

ZHANG, D. W. FU, M. GAO, S. H. LİU, J. L. (2013). Curcumin and diabetes: a systematic review. *Evid Based Complement Alternat Med* , 2013: 636053.