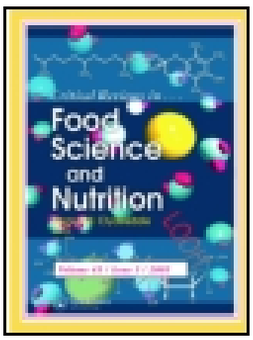

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Curcumin, an Active Component of Turmeric (Curcuma longa), and Its Effects on Health

BetÜl Kocaadam & Nevİn Şanlier

To cite this article: BetÜl Kocaadam & Nevİn Şanlier (2015): Curcumin, an Active Component of Turmeric (Curcuma longa), and Its Effects on Health, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2015.1077195

To link to this article: http://dx.doi.org/10.1080/10408398.2015.1077195

Accepted author version posted online: 03 Nov 2015.

Submit your article to this journal

Article views: 78

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=bfsn20

Download by: [134.117.10.200] **Date:** 18 November 2015, At: 20:14

ACCEPTED MANUSCRIPT

Curcumin, an Active Component of Turmeric (Curcuma Longa), and its Effects on Health

BETÜL KOCAADAM[1] and NEVİN ŞANLIER[1]

[1]Gazi University, Faculty of Health Sciences, Nutrition and Dietetics Department, 06500 Ankara, Turkey

Corresponding Author Email: betulkocaadam@gmail.com

Corresponding Author: Nevin ŞANLIER, Professor, Gazi University, Faculty of Health Sciences, Nutrition and Dietetics Department, Emniyet Mahallesi, Muammer Yaşar Bostancı Caddesi, No:16, 06500 Beşevler /ANKARA, TURKEY

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Turmeric (*Curcuma Longa*) is a type of herb belonging to ginger family, which is widely grown in southern and south western tropical Asia region. Turmeric, which has an importance place in the cuisines of Iran, Malesia, India, China, Polynesia and Thailand, is often used as spice and has an effect on the nature, color and taste of foods. Turmeric is also known to have been used for centuries in India and China for the medical treatments of such illnesses as dermatologic diseases, infection, stress and depression. Turmeric's effects on health generally are centered upon an orange-yellow colored, lipophilic polyphenol substance called 'curcumin', which is acquired from the rhizomes of the herb. Curcumin is known recently to have antioxidant, anti-inflammatory, anti-cancer effects and, thanks to these effects, to have an important role in prevention and treatment of various illnesses ranging notably from cancer to autoimmune, neurological, cardiovascular diseases and diabetic. Furthermore, it is aimed to increase the biological activity and physiological effects of the curcumin on the body by synthesizing

 ACCEPTED MANUSCRIPT

curcumin analogues. This paper reviews the history, chemical and physical features, analogues, metabolites, mechanisms of its physiological activities and effects on health of curcumin.

Key words

Turmeric, curcumin, health, safety

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Downloaded by [134.117.10.200] at 20:14 18 November 2015

1.Introduction

Turmeric is acquired from *Curcuma long L*, a tuberous herbaceous perennial plant with yellow flowers and wide leaves, which is a member of ginger family and grows in tropical climate (Prasad et al., 2014; Akpolat et al.; 2010). Unlike cinnamon, turmeric has not any different kinds; on the other hand, geographical conditions of the region where it grows and the features of its soil may affect the growth, nutrition composition and quality of this plant (Hayakawa et al., 2011; Hossain and Ishimine, 2005). While this plant is a rather important spice in Iran, it is also an important component of curries to which it gives the yellow-color in Malesia, India, China, Polynesia and Thailand; and the mustard and sauces in the West (Gupta et al., 2013a). Turmeric is also used to add flavor and color to rice, pasta, meat and vegetable dishes and salads.

It is stated that turmeric has been widely used for medical treatments of various diseases for at least 2500 years in Asian countries mostly (Gupta et al., 2013a) and it has many benefits for prevention and treatment of many diseases in Ayurveda and traditional Chinese medicine (Deogade and Ghate, 2015). The importance of turmeric in medical treatment primarily stems from orange-yellow colored curcumin, the most active component. Curcumin is a lipophilic polyphenol substance (Jurenka, 2009), which constitutes the 2-5% of turmeric powder (Deogade and Ghate, 2015).

With the studies about curcumin, it has been determined that the chemical structure of this polyphenol substance shows antioxidant, antimicrobial, anti-inflammatory, antiangiogenic, anti-mutagenic, antiplatelet aggregation properties (Deogade and Ghate, 2015; Prasad et al., 2014; Shehzad et al., 2013; Patil et al., 2009). It is stated that, thanks to this properties, curcumin has a

protective and preventive effect against various diseases such as cancer, auto-immune, neurological, metabolic, lung, liver and cardiovascular diseases (Prasad et al., 2014; Gupta et al., 2013b).

Recently, substantial importance has been put on polyphenol substances due to their effects on various degenerative diseases, especially cancer (Sohrab et al., 2013). Examination of the effects of curcumin on health, which is also a polyphenol substance, is highly significant.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

2. Curcumin and Its Historical Process

Curcumin was defined as 'substance that gives the yellow color' by Vogel and Pelletier about 200 years ago. In 1842, it was purely acquired by Vogel Jr. In the mid-1900s, curcumin was stated to be a biologically active component, to have antibacterial property, and therefore, to be effective against *Staphylococcus aureus, Salmonella paratyphi, Mycobacterium tuberculosis and Trichophyton gypseum* types. In 1953, Srinivasan determined the existence of other components called curcuminoids as well as curcumin with the analysis of turmeric through chromatography (Deogade and Ghate, 2015; Prasad et al., 2014; Patil et al., 2009).

Later, curcumin was said to have a cholesterol-lowering, antidiabetic, anti-inflammatory and antioxidant properties; and to have an anticancer activity in both in vitro and in vivo models. Then, with the clinical studies conducted with humans, it was determined that curcumin was safe and effective. FDA (Food and Drug Administration) confirmed curcumin as a compound "generally recognized as safe" (Prasad et al., 2014; Patil et al., 2009)

3. Chemical and Physical Characteristic of Curcumin

The compound of turmeric contains carbohydrate (69.4%), protein (6.3%), fat (5.1%), mineral (3.5%), and moisture (13.1%) (Prasad et al., 2014). The essence of turmeric roots pulverized by drying also contains curcuminoids consisting of curcumin components. Curcuminoids consist of curcumin (77%), demethoxycurcumin (DMC; 17%) and bidemethoxycurcumin (BDMC; 3%) (Goel et al., 2008). It is stated that even if studies focus on curcumin, other curcuminoid components also have biological activities (Shehzad et al., 2010).

Chemical denotation of curcumin is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione or dipheruloylmethane; while its chemical formula is $C_{21}H_{20}O_6$ (Figure 1) (Deogade and Ghate, 2015; Pubchem Open Chemistry Data Base, 2015). Curcumin isn't soluble in water at acidic and neutral pH; however it is soluble in acetone, methanol, ethanol (Goel et al., 2008; Jurenka, 2009). It is stated that curcumin is sensitive to light and therefore it is recommended that biological samples containing curcumin are to be protected from light (Prasad et al., 2014).

4. Curcumin's Natural, Synthetic Analogues, and Metabolites

Due to its insufficient absorption by the body, high metabolism speed and high elimination from the body, curcumin has a limited bioavailability in the body. The low bioavailability of curcumin limits significantly the therapeutics effects of this component (Devassy et al.,2015). Today, new methods have been developed to increase the bioavailability of curcumin. One of these methods is to use piperine with curcumin. It has been shown that piperine increases the bioavailability of curcumin on humans and rats by decreasing glucuronidation of curcumin (Aggarwal and Harikumar, 2009). Use of liposomal curcumin, curcumin nanoparticles, and phospholipid

Downloaded by [134.117.10.200] at 20:14 18 November 2015

complexes are among other methods; besides, it is stated that use of structural analogues of curcumin also increases bioavailability (Devassy et al., 2015, Shehzad et al., 2010).

It is stated that DMC and BDMC, natural analogues of curcumin, has biological activity like curcumin. A study has found that inflammatory transcription factor NF-κB suppression of curcumin is much more effective than others (Curcumin > DMC > BDMC). It is thought that this result may stem from the important role of methoxy groups on the phenyl ring of curcumin (Sandur et al., 2007).

DMC and BDMC have been determined to suppress Inos and COX-2, which are NF-κB onset inflammatory molecules (Guo et al.,2008). Curcumin and DMC have been shown to be effective for decreasing AGEs-originated reactive oxygen types (ROS) in mesangial cells. Curcumin and DMC have also been determined to increase significantly the AGEs decreasing superoxide dismutase activity and malondialdehyde component in the surface of cell culture. It is also stated that these two components provide protection against AGEs-originated apoptosis, and due to these effects, they may provide protection against diabetic neuropathy (Liu et al., 2012).

There are many metabolites of curcumin such as dihydrocurcumin (DHC), tetrahydrocurcumin (THC), octahydrocurcumin (OHC), hexahydrocurcumin (HHC), curcumin glucuronide, curcumin sulfate (Prasad et al.,2014). After many researches on curcumin metabolites, it has been determined that THC shows antioxidant (Murugan and Pari, 2006), anti-inflammatory (Lai et al., 2011), and anticancer (Wu et al., 2011) effects; that HHC has anticancer (Srimuangwong et al.,2012), antioxidant and anti-inflammatory (Li et al., 2012), and platelet aggregation epistasis

Downloaded by [134.117.10.200] at 20:14 18 November 2015

(Dong et al.,2012) properties; that OHC has anti-inflammatory and antioxidant effects (Prasad et al., 2014; Somparn et al., 2007).

Furthermore, synthetic derivatives of curcumin can be acquired with such chemical modifications as phenolic hydroxyl groups, acylation, alkylation, glycosylation and amino acylation (Prasad et al., 2014).

5. Biological Activities and Molecular Targets of Curcumin, and Related Diseases

Downloaded by [134.117.10.200] at 20:14 18 November 2015

In ancient times, curcumin appeared in the Ayurveda medical treatment methods applied in India, used in treatment of injuries, skin diseases, eye infections, ambustions and acne (Hatcher et al., 2008). Curcumin is also an important component of traditional treatment methods called Jiawei-Xiaoyao in China, and it has been used for the treatment of various diseases like dyspepsia, stress, depression for thousands of years (Qin et al., 2009). In the last 30 years, curcumin was shown to have a therapeutic effect against cancer, auto-immune diseases, metabolic diseases, neurological diseases, cardiovascular diseases, lung diseases, liver diseases and a variety of other inflammatory diseases (Aggarwal and Harikumar, 2009; Kannappan et al., 2011).

Curcumin is thought to be effective on pathogenesis of molecular targets with the purpose of prevention and treatment of diseases. It is stated that the modulation of these molecular targets that have a role in the formation process of the disease can be achieved. It has been proven, for instance, that tumor development can be suppressed by suppressing cancer cell signal pathway (Devassy et al., 2015). Curcumin, with its polyphenol structure, is shown to be able to effectively modulate molecular targets that have a role in the pathogenesis of many diseases (Figure 2).

Curcumin has been determined to play an important role regulating cytokines, kinases, enzymes, transcription factors, growth factors, receptors, metastatic and apoptotic molecules in almost all phases of the development of many diseases (Prasad et al., 2014; Baliga et al., 2012; Shehzad and Lee, 2010). The fact that its structure is inclined to high-level methoxylation and low-level hydrogenation gives curcumin a property that increases free radicals scavenging activity. It is stated that this structure probably enables curcumin to have an anticancer, anti-inflammatory and antioxidant effect (Devassy et al., 2015) (Figure 2).

Downloaded by [134.117.10.200] at 20:14 18 November 2015

5.1. Anticancer Effect

Even curcumin has already been shown to have a positive effect against many diseases; its effect against cancer is the most under-researched topic (Devassy et al., 2015). Curcumin has been found to be effective in many phases of cancer development, to suppress transformation, beginning, development and invasion of tumor, angiogenesis and metastasis. Curcumin has been determined to suppress the growth of tumor cells via cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, cIAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53 p21), death receptor pathway (DR4, DR5), and many cell signal pathways that contain protein kinase pathway (JNK, Akt and AMPK) (Ravindran et al., 2009). It is stated that, thanks to these effects of curcumin, it is effective for decreasing or preventing many various cancer types including multiple myeloma and colon, pancreas, breast, prostates, lung, cancers (Devassy et al., 2015; Anand et al., 2008). It is also stated that curcumin increases the effectiveness of radiotherapy and thus, it may open a quicker path to treatment (Akpolat et al., 2010).

In a study dealing with mono carbonyl analogue of B63 acquired through some chemical modifications of curcumin's structure, this component has been shown to have a higher anti-proliferative effect than curcumin on colon cancer cells. At the same time, with the use of less B63 (50 mg/kg B63, 100 mg/kg curcumin), suppression of tumor growth has been achieved like curcumin (Zheng et al., 2014).

5.2. Anti-inflammatory and Antioxidant Effects

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Curcumin has been determined to be an anti-inflammatory and antioxidant agent (Deogade and Ghate, 2015). It is thought that curcumin has these properties due to hydroxyl and methoxy groups (Rahman and Biswas, 2009). Curcumin enables negative regulation of pro-inflammatory interleukins (IL-1, -2, -6, -8, -12), cytokines (tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1)) by causing down-regulation of Janus kinase and Signal Transducer and Activator of Transcription (JAC/STAT) signaling pathway. It is also stated that curcumin regulates the inflammatory response by down-regulating enzymes of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), lipoxygenase, xanthine oxidase activity; and thus, it may cause to suppress activation of nuclear factor kappaB (NF-κB) (Rahman and Biswas, 2009).

Curcumin is stated to show its effectiveness by inhibiting inflammatory cell proliferation, metastasis and angiogenesis through various molecular targets (Shehzad et al., 2013). Large-scale studies have shown that inflammation changes the signal pathways; and thus it is related to the increase of inflammatory biomarkers, lipid peroxides and free radicals. Acute and chronical inflammation is an important risk factor for cardiovascular, neurodegenerative and metabolic

diseases, obesity, type 2 diabetes, and some cancer types (Medzhitov, 2008; Dantzer et al., 2008). Curcumin is stated to be effective for the treatment of various inflammatory diseases such as obesity, diabetes, cardiovascular diseases, neurological diseases, inflammatory bowel disease (Deogade and Ghate, 2015; Prasad et al., 2014; Shehzad et al., 2013).

Curcumin exhibits strong antioxidant effect through free radical-scavenging activity (Deogade and Ghate, 2015). Even though curcumin shows antioxidant effect, in order to increase its antioxidant capacity, analogues of curcumin are focused on. Dolai et al. (2011) showed that the synthetic sugar analogue of curcumin is a stronger antioxidant. It has been determined that while curcumin suppresses tau peptides aggregation and amyloid-β at micromolar concentrations, sugar-curcumin conjugate shows suppressing effect for this aggregation even in nanomolar levels.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

5.2.1. Cardiovascular Diseases

Inflammation has been determined to have a great role in development of cardiovascular diseases (CVD). Curcumin treatment is stated to have an anti-inflammatory effect against CVD, by means of various mechanisms. Curcumin is stated to enable HO-1 expression by actuating Nrf2-dependent antioxidant response element (ARE). It is also stated that curcumin suppress TNF-α in vascular and aortic smooth muscle cells; and that it increases p21 expression through HO-1 (Pae et al., 2007; Wongcharoen and Phrommintikul, 2009). Curcumin treatment on animals has been determined to decrease ischemia through activation of JAK2/STAT3 signal pathway (Duan et al., 2012).

In a study done on rats, it has been proven that applying 50 mg/kg curcumin to rats with salt-sensitivity and hypertensive heart disease develops systolic function and prevents coronary failure (Morimoto et al., 2008). In a study on the effectiveness of curcumin on cardiovascular risk factors in individuals with coronary artery disease, it has been determined that serum triglyceride, LDL and VLDL cholesterol levels decrease considerably in the group of individuals taking curcumin. Even though effects of curcumin on blood lipid profile have been proven, no considerable effect has been determined on inflammatory markers (Mirzabeigia et al., 2015). In a study conducted in Turkey, the consumption prevalence of plant-based alternative treatments and supplementary foods of individuals with cardiovascular diseases was researched; and it was found out that turmeric is one of the most popular herbal foods. Also, hypertension and hyperlipidemia are found to be the most important reasons for patients to use alternative products (İpek et al., 2013).

Downloaded by [134.117.10.200] at 20:14 18 November 2015

5.2.2. Diabetes mellitus

Diabetes mellitus is a health problem affecting liver, heart, brain and kidneys. It has been determined that inflammation is the primary cause of type II diabetes development and that various inflammatory cytokines, transcription factors and enzymes have an important role in the outset and progression of diabetes (Shehzad et al., 2013; Choudhary et al., 2011).

Ghorbani et al. (2014) pointed out that curcumin has such properties as decreasing hepatic glucose production, suppressing inflammatory response stemming from hyperglycemia, increasing GLUT2, GLUT3, GLUT4 gene expression, increasing glucose intake of cells and activating 5' adenosine monophosphate-activated protein kinase (AMPK); and thus, that it may

decrease blood glucose decreasing insulin resistance. They also stated that, for these reasons, curcumin has an increasing effect on anti-hyperglycemic and insulin sensitivity.

One study conducted on type 2 diabetic KK-Ay mice found that curcumin suppresses the increase in blood glucose level via peroxisome proliferator-activated receptor-gamma (PPAR-γ) activation (Kuroda et al., 2005). Studies have been conducted on derivatives of curcumin with the aim of increasing the antidiabetic effect of curcumin. For instance, as a result of a study researching whether a new curcumin derivative (NCD), acquired by covalent modification of curcumin molecule, shows hypoglycemic effect on diabetic rats, it has been proven that NCD decreases plasma glucose level at the rate of 27.5%, and that it increases plasma insulin up to 66.67%. It is stated that NCD shows this effect by inducing HO-1 gene (Aziz et al., 2013; Aziz et al., 2012).

Downloaded by [134.117.10.200] at 20:14 18 November 2015

5.2.3. Obesity

Curcumin has been shown to suppress mitogen-activated protein kinase (MAPK, ERK, JNK, and p38), which is associated with differentiation of 3T3-L1 cells into adipocytes and activates Wnt/β-catenin signaling in differentiated adipocytes., which are closely related to obesity (Ahn et al., 2010). It is stated that curcumin decreases the macrophage infiltration, leptin, leptin receptor level (Ob-R) in the white adipose tissue; that it increases the adiponectin expression in inflammation-related obesity. It is pointed out that the adiponectin production, which increases due to effect of curcumin, may have a positive effect against obesity by decreasing NF-kB activity (Shehzad et al., 2011).

5.2.4. Inflammatory Bowel Disease

Inflammatory bowel disease is an immune impairment including Crohn disease and ulcerative colitis, commonly characterized with digestion system chronical inflammation (Shehzad et al., 2013). Studies indicate that curcumin is useful in prevention and treatment of inflammatory bowel disease (IBD) (Ali et al., 2012; Holt et al., 2005). Curcumin inhibit the activity of activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, PPAR-γ, β-catenin, COX-2, 5-LOX, iNOS expression which play a key role in inflammation (Taylor and Leonard, 2011). Therefore, it can reduce colitis. It has been proven that curcumin, at the same time, suppress TLR4-based NF-kB activation; and thus, it may be effective for recovery of bowel inflammation (Lubbad et al., 2009; Ali et al., 2012; Baliga et al., 2012).

A pilot study done with Crohn or ulcerative patients by Suskind et al. (2013) indicates that recovery in disease symptoms is achieved as a result of using curcumin as 500 mg capcules twice a day during 3 weeks. Researchers have suggested that using curcumin as an adjunctive therapy for the individuals seeking combination of traditional and alternative treatment. Likewise, Taylor and Leonard (2011) have stated that curcumin becomes more effective when used with traditional medicines for the treatment of inflammatory bowel disease; and that this combination is a cheaper alternative method.

5.2.5. Neurodegenerative Diseases

Aging is a significant risk factor for neurodegenerative diseases. It is considered that curcumin may be effective on aging mechanisms; thus, it may prevent the changes in the cell proteins which occur due to aging. Therefore, it is indicated that curcumin may help to maintain protein

Downloaded by [134.117.10.200] at 20:14 18 November 2015

homeostasis and it may be effective for prevention of aging-associated diseases (Monroy et al., 2013). Besides, curcumin has scavenge oxygen derived free radical property; and thus, curcumin is stated to be a potential neuro-protective agent (Nabiuni et al., 2011).

In neurodegenerative diseases as Alzheimer characterized with inflammation and oxidative injury, abnormal protein development causes such gene mutations as human amyloid precursor protein (APP) or presenile 1 or 2 (Smith et al., 2007). In Alzheimer disease, curcumin as an antioxidant, anti-inflammatory properties can improve the cognitive functions, and also it is stated to bring various therapeutic benefits through decreased β-amyloid plaques and microglia formation, delayed deterioration of neurons in patients. (Mishra and Palanivelu, 2008).

Parkinson's disease (PD) one of the most common neurodegenerative diseases is characterized loss of dopaminergic neurons in the substantia nigra. The most important biological effect of curcumin related to neuroprotection is its antioxidant function (Mythri and Srinivas Bharath, 2012). Thus, it protects substantia nigra neurons, ameliorates dopamine levels in the 6-OHDA rat model of PD. İt is pointed out that curcumin protects many tyrosine hydroxylase-positive cells in substantia nigra; and that it maintains the dopamine levels in striatum probably because of this effect (Zbarsky et al., 2005).

Multiple sclerosis is a chronic inflammatory autoimmune disease, characterized with oligodendrocyte in central nervous system and degradation of myelin sheath. Curcumin has been shown to inhibit autoimmune diseases by regulating inflammatory cytokines and associated JAK-STAT, AP-1, NF-kB signaling pathways (Tegenge et al., 2014; Bright, 2007). Th17 cells are important factor for the pathophysiological process of MS. Curcumin suppresses the differentiation and development of Th17 cells through the down-regulation of IL-6, TGF-β, IL-

Downloaded by [134.117.10.200] at 20:14 18 November 2015

1β , IL-23, and STAT3-phosphorylation (Xie et al., 2011). Furthermore, ıt has been determined that curcumin inhibits channel Kv1.3, which is mainly effective on T(EM) cells; and at the same time it suppress the cytokine secretion and proliferation of T(EM) cells which are isolated from multiple sclerosis patients (Lian et al., 2013).

5.2.6. Skin Diseases

The use of curcumin for treatment of skin diseases dates back to ancient times. Due to its role in treatment of skin diseases in India, turmeric is used in production of cream and soap Ayurveda, the ancient Indian medical system, turmeric is widely used as an easy treatment method for eye infections, treat bites, burns, acne (Hatcher et al., 2008; Akpolat et al., 2010).

Today it is indicated that curcumin may be effective against various skin diseases as dermatitis, psoriasis, and scleroderma. It is pointed out that psoriasis, a chronical skin disease, which is characterized with hyper-proliferation and abnormal differentiation of keratinocyte, can be treated by curcumin (Prasad et al., 2014). Curcumin can protect skin by scavenging free radicals and reducing inflammation through nuclear factor-KB inhibition and cytokines (Thangapazham et al., 2007). A study conducted on mice indicates that curcumin diminished psoriasis-like inflammation by reducing cytokines such as IL-1β and IL-6 (Sun et al., 2013).

5.2.7. Allergy and Asthma

Allergy and asthma are pro-inflammatory diseases, stemming from inflammatory cytokines (Shehzad et al., 2013). Turmeric rhizomes have been long used for treatment of allergy and asthma in Asia, especially in India; for treatment of itching and other skin diseases in Thailand (Viswanath and Christy, 2008; Tewtrakul and Subhadhirasakul, 2007). Yano et al. (2000) have indicated that turmeric exhibits anti-allergic activity by suppressing the 48/80-induced histamine

Downloaded by [134.117.10.200] at 20:14 18 November 2015

release from mast cells. The hydroxyl groups of curcumin are indicated to decrease the allergic reactions and to have a positive effect against asthma by broadening the narrowed air pathway and increasing the antioxidant capacity (Shehzad et al., 2013; Viswanath and Christy, 2008). Curcumin has been determined to cause Th2 response down-regulation by decreasing the production of IgE antibodies and cytokine, and enabling the formation of less inflammatory response (Viswanath and Christy, 2008).

6. The Safe Dosage and Toxicology of Curcumin

Curcumin has been confirmed as a 'generally recognized as safe' compound by FDA, and it is stated not to have any toxic effect. According to JECFA and EFSA (European Food Safety Authority) reports, ADI (adequate daily intake) value of curcumin is 0-3 mg/kg (EFSA, 2014; JECFA, 2004;). Lao et al. (2006) applied 500-12000 mg curcumin to healthy individuals so as to examine the maximum tolerance dosage and safety of curcumin. As a result, up to 12 g/day intake of curcumin has been shown to have no harmful effects on individuals. There are some concerns about the relationship between inhibition of some enzymes working in drug metabolism, potential DNA impairment, iron chelation and curcumin intake; however, more studies need to be conducted to examine these relationships (Devassy et al., 2015).

7. Conclusion and Suggestions

In conclusion, the effects of curcumin on health are rather complex as in many other natural products. The results of clinical studies on in vitro, in vivo and human indicate that curcumin may be effective in prevention and treatment of many diseases, particularly cancer, by affecting various molecular targets. Safety, active ingredients, interactions and dosage of the medicine are highly important in treatment of diseases. For this reason, the fact that curcumin is a safe natural

Downloaded by [134.117.10.200] at 20:14 18 November 2015

ACCEPTED MANUSCRIPT

product and its cost is lower than drugs may give rise to the thought that curcumin can be used in treatment and prevention of diseases. Because it prevents formation and progression of various diseases, and has positive effects on health, a healthy individual with a 70 kg body weight can consume 4-10 gram turmeric powder in accordance with JECFA and EFSA's suggestion that curcumin's ADI value should be 0-3 mg/kg. Oral intake of curcumin exhibits poor bioavailability, so it limits significantly the therapeutic effects of this component. Other structural analogues of curcumin are more bioavailable and effective, and they could be designed as to be combined with large and well-controlled clinical trials. It will be good to conduct more studies in order to determine the effectiveness of curcumin, its analogues and metabolites, interaction of drug-food and drug-nutrient more firmly; to clarify the other possible biological activities; to develop suggestions; to provide evidence about its relations with other diseases.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

 ACCEPTED MANUSCRIPT

REFERENCES

Aggarwal BB, Harikumar KB. (2009). Potential therapeutic effects of curcumin, the antiinflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 41:40–59.

Ahn J., Lee H., Kim S., Ha T. (2010). Curcumin-induced suppression of adipogenic differentiation is accompanied by activation of Wnt/beta-catenin signaling. Am. J. Physiol. Cell. Physiol. 298, 1510–1516.

Akpolat M., Tarladaçalışır Y., Uz Y., Metin M., Kızılay G. (2010). Kanser Tedavisinde Curcuminin Yeri. Yeni Tıp Dergisi, 27: 142-147

Ali T., Shakir F., Morton J. (2012). Curcumin and inflammatory bowel disease: biological mechanisms and clinical implication. Digestion 85, 249–255.

Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. (2008). Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer Lett. 267:133–64.

Aziz MT, El-Asmar MF, El-Ibrashy IN, Rezq A, Al-Malki A, Wassef MA, Fouad HH, et al. (2012). Effect of novel water soluble curcumin derivative on experimental type- 1 diabetes mellitus (short term study). Diabetology & Metabolic Syndrome 4:30

Aziz MT, El Ibrashy IN, Mikhailidis DP, Rezq AM, Wassef MA, Fouad HH, Ahmet HH, et al. (2013). Signaling mechanisms of a water soluble curcumin derivative in experimental type 1 diabetes with cardiomyopathy. Diabetol Metab Syndr. 5:13.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Baliga MS, Joseph N., Venkataranganna MV, Saxena A., Ponemone V., Fayad R. (2012). Curcumin, an active component of turmeric in the prevention and treatment of ulcerative colitis: preclinical and clinical observations. Food Funct;3:1109–17.

Bright J. (2007). Curcumin and Autoimmune Disease. Adv Exp Med Biol. 595:425-51.

Choudhary S., Sinha S., Zhao Y., Banerjee S., Sathyanarayana P., Shahani S., et al. (2011). NF-kappaB-inducing kinase (NIK) mediates skeletal muscle insulin resistance: blockade by adiponectin. Endocrinology 152, 3622–3627

Dantzer R., O'Connor J. C., Freund G., Johnson W., Kelley W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.

Devassy J., Nwachukwu I., Jones P. (2015). Curcumin and cancer: barriers to obtaining a health claim. Nutrition Reviews Vol. 73(3):155–165.

Deogade S. and Ghate S. (2015). Curcumın: Therapeutıc Applıcatıons In Systemıc And Oral Health. International Journal of Biological & Pharmaceutical Research. 6(4): 281-290.

Dolai S, Shi W, Corbo C, Sun C, Averick S, Obeysekera D, et al. (2011). "Clicked" sugar–curcumin conjugate: modulator of amyloid-beta and tau peptide aggregation at ultralow concentrations. ACS Chem Neurosci. 2:694–9.

Dong HP, Yang RC, Chunag IC, Huang LJ, Li HT, Chen HL, Chen CY. (2012). Inhibitory effect of hexahydrocurcumin on human platelet aggregation. Natural Product Communications 7(7):883-884

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Duan W., Yang Y., Yan J., Yu S., Liu J., Zhou J., et al. (2012). The effects of curcumin post-treatment against myocardial ischemia and reperfusion by activation of the JAK2/STAT3 signaling pathway. Basic Res Cardiol.107:263

European Food Safety Authority (2014). Refined exposure assessment for curcumin (E 100). EFSA Journal 12(10):3876

Ghorbani Z., Hekmatdoost A., Mirmiran P. (2014). Anti-Hyperglycemic and Insulin Sensitizer Effects of Turmeric and Its Principle Constituent Curcumin. Int J Endocrinol Metab. October,12(4): e18081.

Guo LY, Cai XF, Lee JJ, Kang SS, Shin EM, Zhou HY, et al. (2008). Comparison of suppressive effects of demethoxycurcumin and bisdemethoxycurcumin on expressions of inflammatory mediators in vitro and in vivo. Arch Pharm Res, 31:490–6.

Gupta SC, Sung B, Kim JH, Prasad S, Li S, Aggarwal BB. (2013a). Multitargeting by turmeric, the golden spice: From kitchen to clinic. Mol Nutr Food Res. 57(9):1510–28.

Gupta SC, Kismali G, Aggarwal BB. (2013b). Curcumin, a component of turmeric: from farm to pharmacy. Biofactors.;39(1):2–13.

Goel A, Kunnumakkara AB, Aggarwal BB. (2008). Curcumin as “Curecumin”: from kitchen to clinic. Biochem Pharmacol. 75:787–809.

Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. (2008). Curcumin: from ancient medicine to current clinical trials. Cell Mol Life Sci. 65:1631–1652.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

ACCEPTED MANUSCRIPT

Hayakawa H., Kobayashi T., Minamiya Y., Ito K., Miyazaki A., Fukuda T., Yamamoto Y., (2011). Development of a Molecular Marker to Identify a Candidate Line of Turmeric (Curcuma longa L.) with a High Curcumin Content. American Journal of Plant Siences, Vol. 2, No. 1, pp. 15-26

Holt p., Katz S., Kirshoff R. (2005). Curcumin Therapy in Inflammatory Bowel Disease: A Pilot Study. Digestive Diseases and Sciences, Vol. 50, No. 11 pp. 2191–2193

Hossain A., Ishimine Y. (2005). Growth, Yield and Quality of Turmeric (Curcuma longa L.) Cultivated on Dark-red Soil, Gray Soil and Red Soil in Okinawa, Japan. Plant. Prod. Sci. 8 (4): 482-486

İpek E., Güray Y., Demirkan B., Güray Ü., Kafes H., Başyiğit F. (2013). Kardiyoloji Polikliniğine Başvuran Hastalarda Bitkisel Kökenli Alternatif Tedavilerin ve Tamamlayıcı Besin Ürünlerinin Tüketim Prevalansı. Arch Turk Soc Cardiol. 41(3):218-224

JECFA (2004). Curcumin. (Prepared by Ivan Stankovic). Chemical and Technical Assessment Compendıum Addendum 11/Fnp 52 Add.11/29; Monographs 1 Vol.1/417.

Jurenka JS. (2009). Anti-inflammatory properties of curcumin, a majör constituent of *Curcuma longa*: a review of preclinical and clinical research. Altern Med Rev.14(2):141–53.

Kannappan R, Gupta SC, Kim JH, Reuter S, Aggarwal BB. (2011). Neuroprotection by spice-derived nutraceuticals: you are what you eat! Mol Neurobiol. 44:142–59.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

 ACCEPTED MANUSCRIPT

Kuroda M., Mimaki Y., Nishiyama T., Mae T., Kishida H., Tsukagawa M., Takahashi K., Kawada T., Nakagawa K., Kitahara M. (2005). Hypoglycemic effects of turmeric (Curcuma longa L. rhizomes) on genetically diabetic KK-Ay mice. Biol Pharm Bull. 28(5):937-9.

Lai CS, Wu JC, Yu SF, Badmaev V, Nagabhushanam K, Ho CT, Pan MH. (2011). Tetrahydrocurcumin is more effective than curcumin in preventing azoxymethane-induced colon carcinogenesis. Mol Nutr Food Res. 55:1819–28.

Lao CD., Ruffin MT., Normolle D., Heath DD., Murray SI., et al. (2006). Dose escalation of a curcuminoid formulation. BMC. Complementary and Alternative Medicine. 6, 10.

Li F, Nitteranon V, Tang X, Liang J, Zhang G, Parkin KL, Hu Q. (2012). In vitro antioxidant and antiinflammatory activities of 1-dehydro-[6]-gingerdione, 6-shogaol, 6-dehydroshogaol and hexahydrocurcumin. Food Chem. 135:332–7.

Lian YT, Yang XF, Wang ZH, Yang Y, Yang Y, Shu YW, Cheng LX., Liu K. (2013). Curcumin serves as a human kv1.3 blocker to inhibit effector memory T lymphocyte activities. Phytother Res. 27:1321–7.

Liu JP, Feng L, ZhuMM, Wang RS, Zhang MH, Hu SY, et al. (2012). The in vitro protective effects of curcumin and demethoxycurcumin in *Curcuma longa* extract on advanced glycation end products-induced mesangial cell apoptosis and oxidative stress. Planta Med, 78:1757–60.

Lubbad A., Oriowo A., Khan I. (2009). Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis. Mol. Cell. Biochem. 322, 127–135.

Medzhitov R. (2008). Origin and physiological roles of inflammation. Nature 454, 428–435.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Mirzabeigia P., Mohammadpour AH, Salarifar M., Gholami K., Mojtahedzadeh M., Javadi MR (2015). The Effect of Curcumin on some of Traditional and Non-traditional Cardiovascular Risk Factors: A Pilot Randomized, Double-blind, Placebo-controlled Trial. Iranian Journal of Pharmaceutical Research 14 (2): 479-486

Mishra S., Palanivelu K. (2008). The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Ann Indian Acad Neurol. 2008 Jan-Mar; 11(1): 13–19.

Morimoto T., Sunagawa Y., Kawamura T., Takaya T., Wada H., Nagasawa A., et al. (2008). The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J. Clin. Invest. 118, 868–878.

Monroy A., Lithgow GJ, Alavez S. (2013). Curcumin and neurodegenerative diseases. Biofactors. 39(1): 122–132.

Murugan P., Pari L. (2006). Antioxidant effect of tetrahydrocurcumin in streptozotocin–nicotinamide induced diabetic rats. Life Sciences. Volume 79, Issue 18, pp:1720–1728

Mythri RB., Srinivas Bharath MM. (2012). Curcumin: A Potential Neuroprotective Agent in Parkinson's Disease. Current Pharmaceutical Design, 18, 91-99

Nabiuni M., Nazari Z., Abdolhamid Angaji S., Nejad S. (2011). Neuroprotective Effects Of Curcumin. Australian Journal of Basic and Applied Sciences, 5(9): 2224-2240

Pae O., Jeong S., Jeong O., Kim S., Kim A., et al. (2007). Roles of heme oxygenase-1 in curcumin-induced growth inhibition in rat smooth muscle cells. Exp. Mol. Med. 39, 267–277.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Patil P., Jayaprakasha GK., Chidambara Murthy KN. (2009). Vıkram A. Bioactive Compounds: Historical Perspectives, Opportunities, and Challenges. J. Agric. Food Chem. 2009, 57, 8142–8160

Pubchem Open Chemistry Data Base, 'Curcumin'. (2015). Access Date:22.07.2015 http://pubchem.ncbi.nlm.nih.gov/compound/curcumin#section=Top

Prasad S., Gupta S., Tyagi A., Aggarwal B. (2014). Curcumin, a component of golden spice: Frombedside to bench and back. Biotechnology Advances. 32, 1053–1064.

Qin F., Huang X., Zhang H.M., Ren P. (2009). Pharmacokinetic comparison of puerarin after oral administration of Jiawei- Xiaoyao-San to healthy volunteers and patients with functional dyspepsia: influence of disease state. J. Pharm. Pharmacol., 61, 125-129.

Rahman I, Biswas SK. (2009). Regulation of Inflammation, Redox, and Glucocorticoid Signaling by Dietary Polyphenols. In: Surh YJ, Dong Z, Cadenas E, Packer L editors. Boca Raton: CRC Press

Ravindran J, Prasad S, Aggarwal BB. (2009). Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? AAPS J. 11:495–510.

Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, et al. (2007). Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS independent mechanism. Carcinogenesis. 28:1765–73.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

ACCEPTED MANUSCRIPT

Shehzad A., Ha T., Subhan F., and Lee S. (2011). New mechanism and anti-inflammatory role of curcumin in obesity and obesity related metabolic disease. Eur. J. Nutr. 50, 151–161.

Shehzad A., Khan S., Shehzad O., Lee YS. (2010). Curcumin Therapeutic Promises And Bioavailability In Colorectal Cancer. Drugs of Today, 46(7): 523-532

Shehzad A., Lee YS. (2010). Curcumin: multiple molecular targets mediate multiple pharmacological actions—a review. Drugs Fut. 35, 113–119.

Shehzad A., Rehman G., Lee Y. (2013). Curcumin in Inflammatory Diseases. International Union of Biochemistry and Molecular Biology, Inc. Volume 39, Number 1, Pages 69–77.

Smith G., Cappai R., Barnham J. (2007) The redox chemistry of the Alzheimer's disease amyloid beta peptide. Biochim. Biophys. Acta. 1768, 1976–1790.

Srimuangwong K., Tocharus C., Yoysungnoen Chintana P., Suksamrarn A., Tocharus J. (2012). Hexahydrocurcumin enhances inhibitory effect of 5-fluorouracil on HT-29 human colon cancer cells. World J Gastroenterol. 18:2383–9.

Sohrab G, Hosseinpour-Niazi S, Hejazi J, Yuzbashian E, Mirmiran P, Azizi F. (2013). Dietary polyphenols and metabolic syndrome among Iranian adults. Int J Food Sci Nutr. 64(6):661–7.

Somparn P, Phisalaphong C, Nakornchai S, Unchern S, Morales NP. (2007). Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull. 30:74–8.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

 ACCEPTED MANUSCRIPT

Sun J, Zhao Y, Hu J. (2013). Curcumin inhibits imiquimod-induced psoriasis-like inflammation by inhibiting IL-1beta and IL-6 production in mice. PLoS One. 8:e67078.

Suskind DL., Wahbeh G., Burpee T., Cohen M., Christie D., Weber W. (2013). Tolerability of curcumin in pediatric inflammatory bowel disease: a forced-dose titration study. J Pediatr Gastroenterol Nutr. 56:277–9.

Taylor RA, Leonard MC. (2011). Curcumin for inflammatory bowel disease: a review of human studies. Altern Med Rev. 16:152–6..

Tegenge MA, Rajbhandari L., Shrestha S., Mithal A., Hosmane S., Venkatesan A. (2014). Curcumin protects axons from degeneration in the setting of local neuroinflammation. Exp Neurol. 253C:102–10.

Tewtrakul S., Subhadhirasakul S. (2007). Anti-allergic activity of some selected plants in the Zingiberaceae family. Journal of Ethnopharmacology 109 (535–538).

Thangapazham RL, Sharma A., Maheshwari RK. (2007). Beneficial role of curcumin in skin diseases. Adv Exp Med Biol. 595:343-57.

Viswanath PK., Christy SB. (2008). Immunomodulatory effects of curcumin in allergy. Mol. Nutr. Food Res. 52, 1031–1039.

Wongcharoen W., Phrommintikul A. (2009). The protective role of curcumin in cardiovascular diseases. Int. J. Cardiol. 133, 145–151.

Downloaded by [134.117.10.200] at 20:14 18 November 2015

Wu JC, Lai CS, Badmaev V., Nagabhushanam K., Ho CT, Pan MH. (2011). Tetrahydrocurcumin, a major metabolite of curcumin, induced autophagic cell death through coordinative modulation of PI3K/Akt-mTOR and MAPK signaling pathways in human leukemia HL-60 cells. Mol Nutr Food Res. 55:1646–54.

Xie L., Li a X., Takahara S. (2011). Curcumin has bright prospects for the treatment of multiple sclerosis. International Immunopharmacology 11 323–330

Yano, S., Terai, M., Shimizu, K. L., Futagami, Y., Sekine, T., et al. (2000). Antiallergic activity of Curcuma longa. (II). Features of inhibitory actions on histamine release from mast cells. Natural Medicines. 54, 325–329.

Zbarsky V., Datla KP, Parkar S., Rai DK, Aruoma OI, Dexter DT. (2005). Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. Free Radic Res. 39(10):1119-25.

Zheng A, Li H,Wang X, Feng Z, Xu J, Cao K, et al. (2014). Anticancer effect of a curcumin derivative B63: ROS production and mitochondrial dysfunction. Current Cancer Drug Targets, 14, 156-166

Downloaded by [134.117.10.200] at 20:14 18 November 2015

ACCEPTED MANUSCRIPT

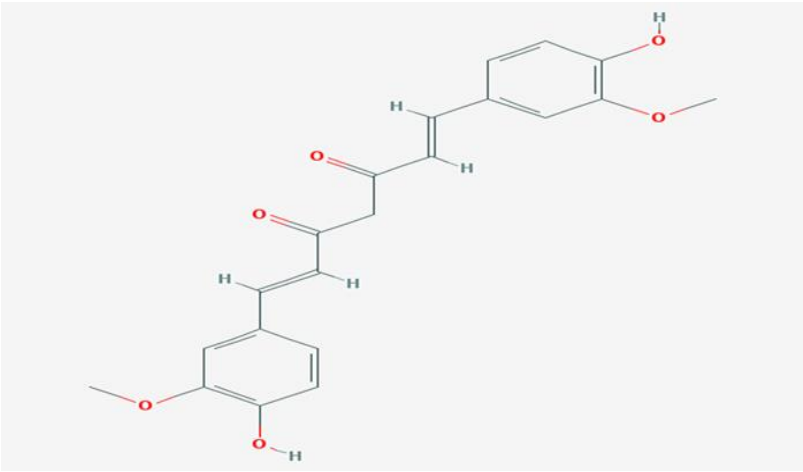

Figure 1. Chemical Structure of Curcumin

Downloaded by [134.117.10.200] at 20:14 18 November 2015

 ACCEPTED MANUSCRIPT

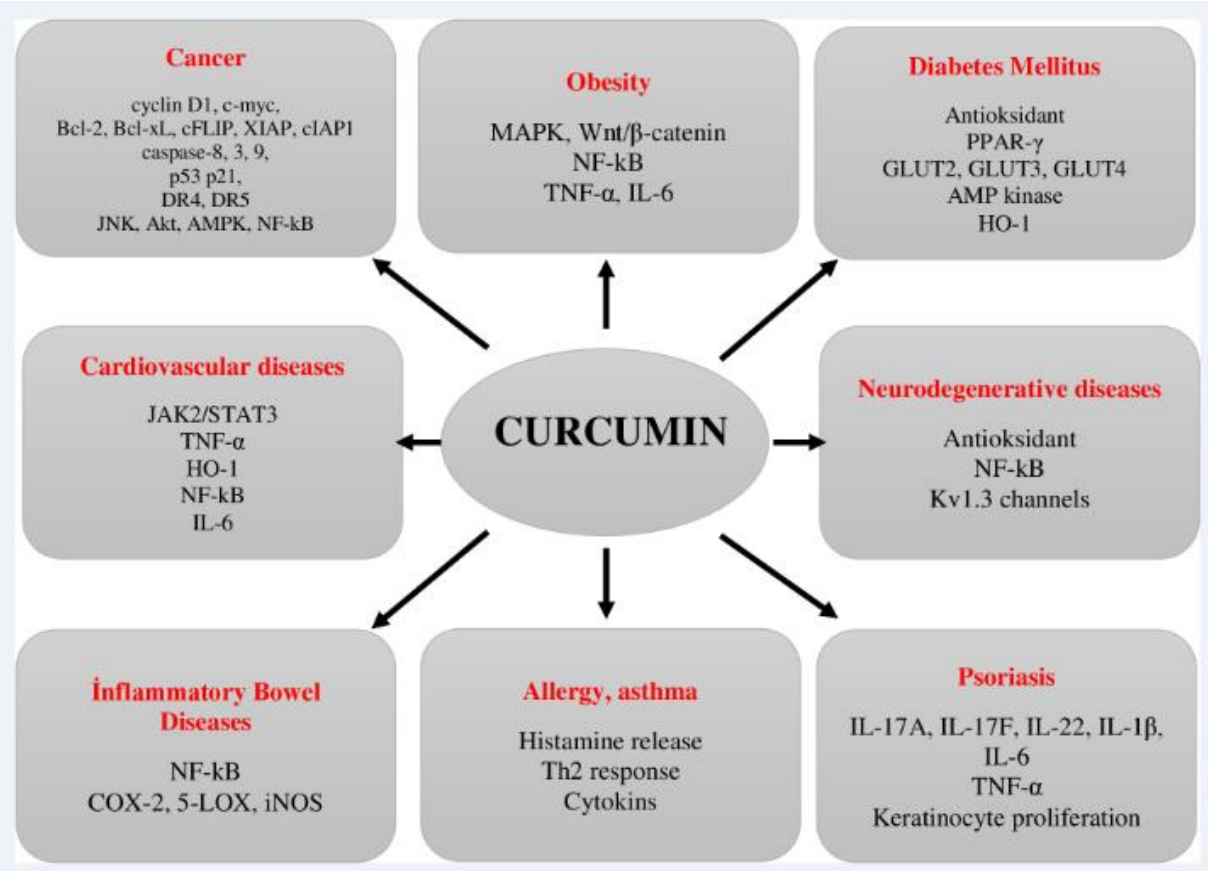

Figure 2. Related Molecular Targets and Diseases of Curcumin

Downloaded by [134.117.10.200] at 20:14 18 November 2015