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REVIEW PAPER

An overview of the biological function of curcumin in the processes of oxidative stress, inflammation, nervous system, and lipid levels

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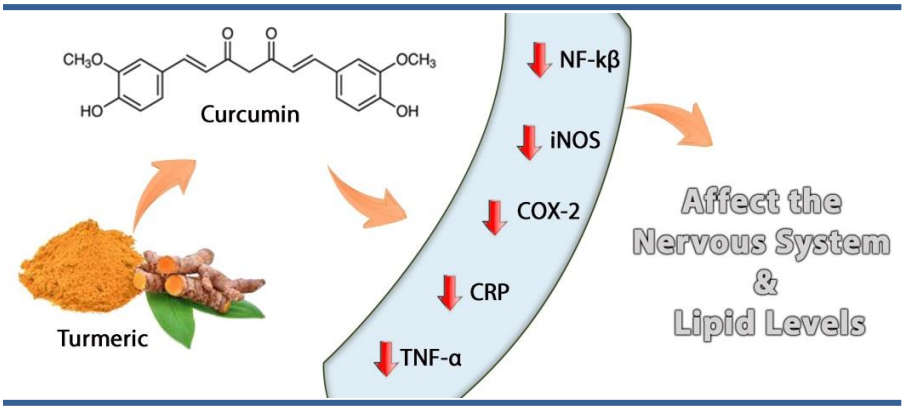
Highlights

- Curcumin as a herbal substance has received much consideration in the field of research.
- Curcumin has anti-inflammatory and anti-oxidative stress influences.
- Curcumin can affect the nervous system and lipid levels.

Graphical Abstract



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Abstract

Recently, treatment with antioxidants, especially herbal therapy, has been widely studied to prevent the occurrence of many diseases. Turmeric with the scientific name Curcuma longa from the Zingiberaceae family is one of the oldest plants that have been applied in traditional medicine. It has been abundant and it has been used to protect many tissues from different damage. Many researches have been reported on curcumin's antioxidant, anti-cancer and anti-inflammatory, features. Curcumin clearly shows antioxidant and free radical scavenging effects in vivo and in vitro conditions. This compound can protect normal cells from the attack of reactive oxygen species by neutralizing oxidative damage. The anti-inflammatory impacts of curcumin have been established in numerous researches via different pathways. Curcumin directly binds to small beta-amyloids and prevents the accumulation and formation of fibrils in vitro and in vivo. Thus it can be the cause of its effect in Alzheimer's disease. Curcumin significantly reduces the level of LDL and VLDL in the plasma and causes a decrease in the total level of cholesterol in the liver. In this study, we intend to describe the biological features of curcumin as a natural substance in processes such as oxidative stress, inflammation, nervous system, and lipid levels.

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Introduction

Although the progress of mankind made it away from nature, today mankind has again turned to use this resource in various fields, especially in the field of treatment. The trend toward fields such as herbal medicines has increased. Turmeric is one of the plants that are not only used for food but also for treatment aims. One of the compounds found in the underground stem of this plant is curcumin. Curcumin, which is a yellow substance in turmeric, has a history of more than 5,000 years. Turmeric is acquired from the underground stem of the Curcuma longa plant, which is an evergreen plant and it has been used not only as a spice but also as a treatment for many ailments. This plant is cultured in Asia and Southeast Asia. In China and India, it is used as a treatment for toothache, anorexia, cough, liver diseases, and sinusitis (1, 2).

The therapeutic use of curcumin is not a new thing and it has been used as a traditional treatment of this substance in both Indian and Chinese medicine and has been employed as an antiseptic, pain reliever, anti-inflammatory, antioxidant and anti-malarial agent (3). Turmeric has caused the healing of infectious and non-infectious wounds in mice and rabbits. It has had a protective effect in oral and early stomach cancer models in mice and hamsters. Curcumin has increased mucin secretion in rabbits. Curcumin has been effective in arthritis caused by formalin. This substance improves the function of the intestine and elevates the activity of pancreatic enzymes such as chymotrypsin, and trypsin, amylase. Curcumin and ethanol extract of Curcuma longa has a lipid-reducing effect in mice. Curcumin also has antibacterial, anti-amoebic, and anti-HIV effects (4-8).

Curcumin as the active ingredient of turmeric has many biological properties. Among these properties, we can mention the effect on the nervous system, antioxidant and anti-inflammatory activity, etc (9). Curcumin directly binds to small beta-amyloids and prevents the accumulation and formation of fibrils in vivo and in vitro. This information indicates that a small amount of curcumin effectively prevents the accumulation of beta-amyloids and their fibril formation and oligomerization.

It can be the cause of its effect in Alzheimer's disease (10). Curcumin truly reduces the level of LDL and VLDL in the plasma and causes a decrease in the total level of cholesterol in the liver along with an elevation in α-tocopherol in the plasma (11). Curcumin clearly shows antioxidant and free radical scavenging effects in vivo and in vitro conditions. This compound can protect normal cells from the attack of reactive oxygen species (ROS) by neutralizing oxidative damage. It has been deduced that the activity of antioxidant and scavenging of free radicals of phenolic CH or the OH group of curcumin is due to the groups of the beta-diketone part of the molecule. Free radicals are neutralized and deactivated by receiving a proton from curcumin or by receiving an electron from this compound (12-14).

The anti-inflammatory impacts of curcumin have been established in several researches. Some of the anti-inflammatory effects of curcumin are as follows; Suppression of NF-κB transcription factor, which regulates the activity of pro-inflammatory factors. Inhibiting the production of COX-2, which is an enzyme that has a function in many inflammatory pathways. It blocks the pro-inflammatory enzyme 5-LOX expression and it has been shown that curcumin can attach to the active part of 5-LOX and block it. This compound reduces the number of molecules in the cell surface that are related to inflammation. Curcumin can reduce inflammatory factors including IL-1, IL-6, IL-8, TNF, and chemokines. Curcumin can prevent the activity of TNF, which is the most important inflammatory cytokine (15-17). Considering the expansion of human approach to herbal therapy, in this study we intend to describe the biological features of curcumin as a natural substance in processes such as oxidative stress, inflammation, nervous system, and lipid levels.

Curcumin as an herbal compound

Turmeric is an underground plant stem from the ginger family, which is called Curcuma and Turmeric in Latin. Turmeric is an herbaceous plant, stable, one to one and a half meters high, and has a swollen rhizome from which aerial stems emerge. This plant grows in the eastern regions of India and China, but it is also grown in many tropical places such as Malaysia, Pakistan, Indonesia, Africa, and South America, and its propagation is done, and like ginger, it is propagated by planting parts of the sprouted rhizome of the plant, and due to its

unique health-giving properties, it is known as a functional food all over the world. The turmeric plant traditionally has several applications uses in the food and pharmaceutical industries. The antioxidant, antibacterial, and anti-cancer features of turmeric rhizome have been proven (18).

Curcumin or diferuloylmethane (C12H20O6) is a polyphenol with hydrophobic features derived from the turmeric rhizome. The rhizome of turmeric comprises three main analogues: curcumin, bisdemethoxycurcumin, and demethoxycurcumin, which are totally named curcuminoids. These compositions are different from each other in the methoxy group position on the ring of aromatic. Among these three curcuminoids, curcumin is the most plentiful in turmeric. Curcumin has a suitable yellow color, which makes it possible to use it as a coloring agent in the food industry to make one of the most widely used spices (9, 19).

The date of curcumin discovery is about 200 years ago and it was first isolated in crude form in 1815 by Pelletier and Vogel from the rhizome of Curcuma longa. In 1842, a pure form of curcumin was obtained by Vogel, but its formula was not determined. In 1910, the structure and chemical formula of curcumin were identified by Milobedzka and colleagues, and in 1913, this compound was synthesized by Lampe and Milobedzka. In 1953, the components of curcumin were measured and separated by chromatography by Srinivasan. This compound is insoluble in ether and water and soluble in ethanol and dimethyl sulfoxide (DMSO) or dimethyl sulfoxide and acetone (2, 5, 20-22).

Pure curcumin is a crystalline powder insoluble in water and easily dissolves in solvents such as acetone and methanol. Curcumin has remarkable functional properties and in the research, several properties of this compound such as anti-tumor activity, reduction of liver and blood cholesterol, increase of the function of immune system, prevention of cardiovascular diseases, inhibition of biological membrane injury *vs*. peroxidation, anti-inflammatory features, and reduction of rheumatic arthritis, protection *vs*. Alzheimer's disease, defensive impacts *vs*. aflatoxin B1, and antioxidant properties have been reported (23, 24).

Structurally, curcumin has two phenolic rings in its molecule, while butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) have only one phenolic ring, so curcumin can have stronger antioxidant activity than them (25). Curcumin is also known as a health-giving compound. Research has shown that curcuminoids trap free radicals and types of ROS including peroxynitrite, peroxyl radicals, superoxide radicals, and hydroxyl radicals, whose products are effective in inducing and causing oxidation. Curcuminoids effectively neutralize the 1,1-diphenyl-2-picrylhydrazyl (DPPH) established free radical and this reaction is often used to compare the antioxidant activity of different compounds (26).

Researchers believe that curcumin through trapping and stabilizing all kinds of free radicals, such as peroxyl radicals of lipid, can prevent the spread of oxidation, and this action can be done by providing a hydrogen atom. Curcumin is unique due to the fact that it has both a phenolic ring and a B-diketone part on one molecule because both of these groups cause antioxidant activity. Some researchers claim that curcumin donates hydrogen atoms from phenolic groups, while others believe that hydrogen originates from the central methylene group (27-29).

Therapeutic and biological features of curcumin

Despite the nutritional and treatment usage of curcumin for many years in different nations, the biological properties of this compound were not truly determined till the middle of the twenty century, until it was first reported in 1949 that curcumin is an active biological component with anti-microbial features (5). Recently, numerous researches have shown that this compound has antioxidant, anti-inflammatory, antiviral, antifungal, antibacterial, anti-proliferative, anti-apoptotic, etc. influences and has great therapeutic potential effects against diseases such as neurodegeneration, depression, kidney poisoning, intestinal inflammation, allergies, psoriasis, diabetes, arthritis, AIDS, and especially cancer (30, 31). The anti-cancer influences of turmeric are important in the sense that the consumption of this substance in high doses prevents the proliferation of cancer cells, but it does not harm healthy cells (32).

Cancer is caused by disturbances in the regulation of cell signaling pathways in different stages. Considering that most diseases and especially cancer are caused by the disturbance in the regulation of more than five hundred various gene productions, inhibiting a single gene production or a signaling path is not a very suitable solution in cancer treatment. Most of the current anticancer treatments are involved in modulating or inhibiting a single target and are called single target therapies. Some of these treatments are not very safe treatments due to inefficiency, lack of safety and high cost; therefore, many pharmaceutical companies have turned to the development of multi-target treatments (33, 34).

Considering the complexity and the involvement of multiple signaling pathways in the progression and development of cancer, a drug must be designed that can interact with multiple molecules. Many herbal products, including curcumin, are naturally multitarget and can be cheaper, safer, and more effective compared to synthetic drugs. The multitarget nature of curcumin is the key to its therapeutic potential against cancer and many diseases. Curcumin's anti-cancer potential against several kinds of cancers such as breast, genitourinary, gastrointestinal, lymphoma, leukemia, uterine, ovary, and lung cancers, melanoma, colon, sarcoma, brain tumors, etc. have been shown.

The mechanisms by which curcumin inhibits tumor formation include a combination of antioxidant, anti-inflammatory, anti-angiogenesis, anti-metastasis, and inhibition of the cell cycle that induces its inhibitory effects on cancer through the regulation of genes and molecules involved in these pathways (35, 36). The anti-cancer and anti-inflammatory impacts of curcumin are chiefly due to its antioxidant influences and its impacts on cell enzymes, prevention of signaling pathways at various stages, cell adhesion and angiogenesis. Curcumin is associated with protein kinase C and calcium regulation. An increase in cytosol calcium may cause an elevation in ROS and the antioxidant and antiangiogenic effect of curcumin is to inhibit the entry of calcium. Several types of research have been conducted on the unique antioxidant properties, anti-mutation effect, and anti-tumor effect. Curcumin has anti-carcinogenic and anti-cholesterol influences (37).

The antioxidant effect of curcumin is equal to vitamins E and C. By inhibiting the angiogenesis of cancer tissue, curcumin decreases the tumor cells growth and also reduces the activity of telomerase in these cells. This substance inhibits angiogenesis in tumors via blocking the vascular endothelial growth factor (VEGF) and stopping their growth (37, 38). Also, in the animal model of inflammation, curcumin inhibits metabolism of arachidonic acid and inflammation in epidermis of mouse by reducing the activity of cyclooxygenase and lipoxygenase pathways (39).

Antioxidant feature of curcumin

Curcumin clearly shows antioxidant and free radical scavenging effects in vivo and in vitro conditions. This compound can protect normal cells from the attack of ROS by neutralizing oxidative damage. It has been deduced that the antioxidant activity and free radicals scavenging of phenolic CH or the OH group of curcumin is due to the groups of the beta-diketone part of the molecule. Free radicals are neutralized and deactivated by receiving a proton from curcumin or by receiving an electron from this compound (13). Of course, it has been proven that curcumin has the ability to receive electrons and regenerate itself (40).

Curcumin exerts its antioxidant effects, especially in vivo environments, through other mechanisms. This compound shows antioxidant effects mainly by inhibiting nitric oxide, hydrogen peroxide, and superoxide radicals (2). It has been described that this compound also increases the activity of several antioxidant enzymes including superoxide dismutase, catalase, heme oxygenase, and glutathione peroxidase, thus preventing lipid peroxidation. In addition, this compound increases the detoxifying enzymes activity in the liver and kidney and protects normal cells from carcinogenesis processes. Also, curcumin increases the activity of other enzymes including glutathione transferase and increases the amount of reduced glutathione and free sulfhydryl groups, and finally raises the antioxidant level of the in vivo environment (41, 42). The schematic of antioxidant activity of curcumin is depicted in Figure 1.

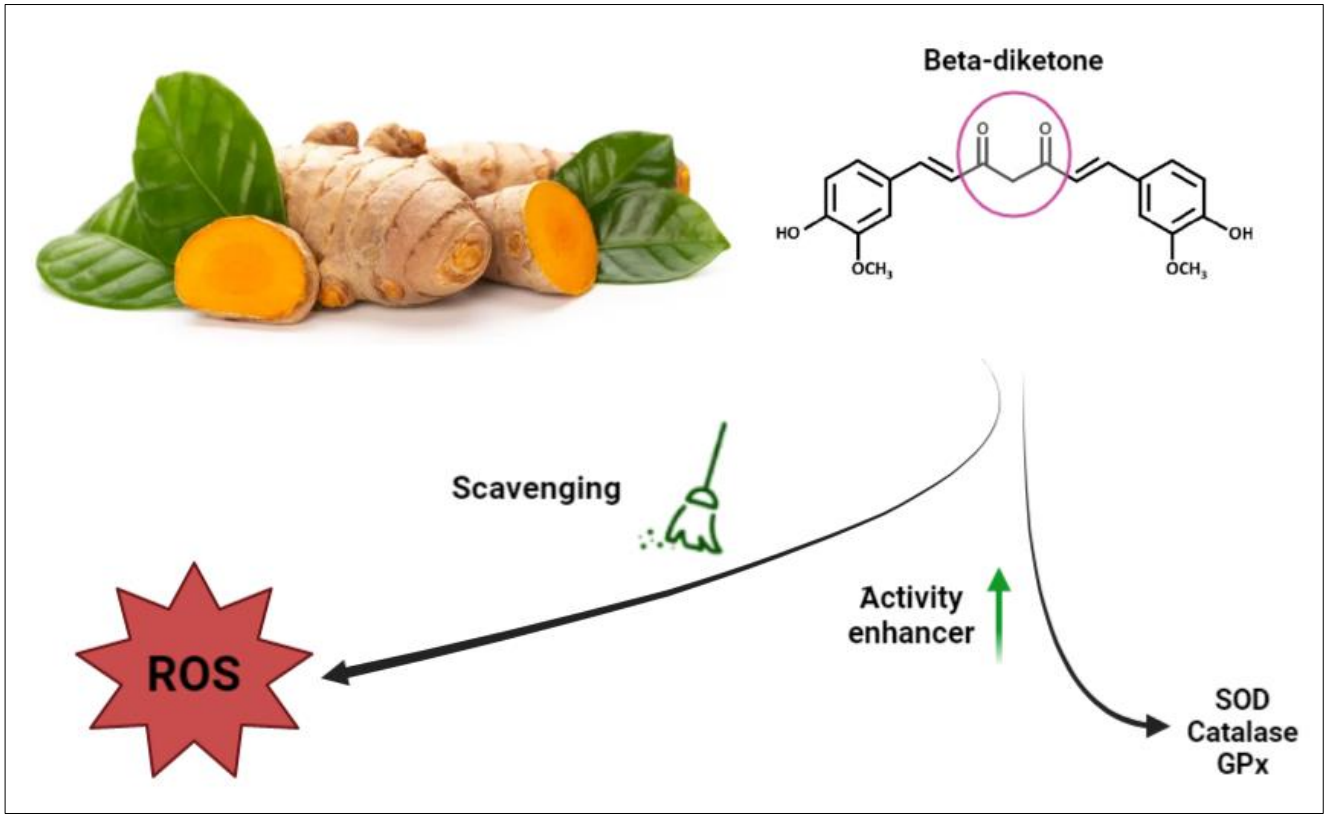

Figure 1. Antioxidant activity of curcumin.

Free radicals scavenging of phenolic CH or the OH group of curcumin is due to the groups of the beta-diketone part of the molecule. Curcumin also increases the several antioxidant enzymes activity including superoxide dismutase, catalase, and glutathione peroxidase.

Anti-inflammatory properties of curcumin

The anti-inflammatory impacts of curcumin have been established in several researches. Since oxidative stress results in chronic inflammatory disorders, antioxidant compounds could be beneficial in the inhibition and therapy of inflammatory diseases (15). Curcumin exhibits high antioxidant activity. The answer to the question of whether the anti-inflammatory function of this compound depends on its antioxidant action is not so easy. Since several antioxidants have anti-inflammatory features, it is improbable that the influences of anti-inflammatory of this compound are only because of its antioxidant features. Curcumin, as a strong anti-inflammatory agent, exerts its impacts via various mechanisms (43).

First, curcumin prevents the NF-kβ factor activation, which induces pro-inflammatory gene products (44). Second, curcumin reduces the expression of inflammatory enzymes such as inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX-2), which play a role in many inflammations (45). Third, curcumin binds to the active site of another pro-inflammatory enzyme called 5-lipoxygenase (LOX) and thus inhibits the expression and activity of this enzyme (46). Fourth, curcumin reduces the expression of several molecules attached to the cell surface that bind to inflammatory mediators. Fifth, curcumin reduces the CRP expression and several inflammatory cytokines such as IL-8, IL-6, IL-1, and chemokines (47). Sixth, curcumin prevents the TNF-α activity, which is one of the most vital mediators of pro-inflammation process (48). In addition, curcumin prevents the proliferation and migration of T lymphocytes (Figure 2) (49).

According to research results, the active substance of turmeric or curcumin has high reactivity with molecules involved in inflammation and inflammatory responses by reducing the activity of nitric oxide synthase, lipoxygenase, and cyclooxygenase 2 enzymes and reducing the generation of inflammatory cytokines including TNF-α and IL-1, IL-2, IL-6, IL-8, and IL-12. Curcumin prevents the expression of nuclear factor KB

and inhibits the process of inflammation and tumorigenesis. Therefore, in addition to inflammatory processes, this compound also prevents the generation of pro-inflammatory cytokines (15).

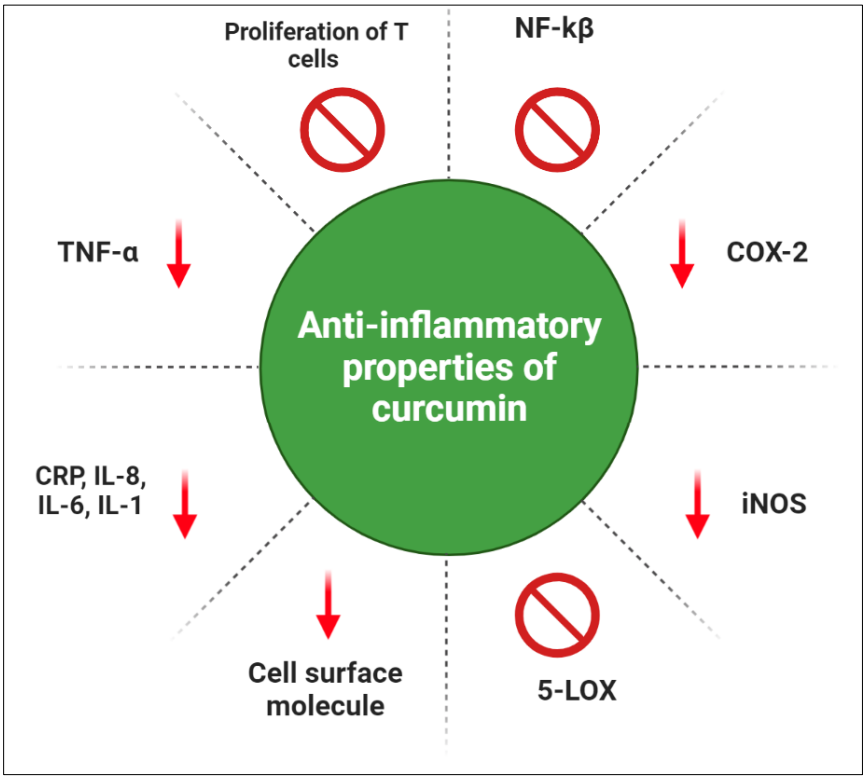

Figure 2. Mechanisms of action of curcumin as an anti-inflammatory compound.

Curcumin prevents the NF-kβ activation, reduces the expression of iNOS, and COX-2, inhibits 5-lipoxygenase (LOX), reduces the expression of variuos molecules attached to the cell surface that bind to inflammatory mediators, reduces the expression of CRP and several inflammatory cytokines such as IL-8, 6, 1, and chemokines, inhibits the activity of TNF-α, and blocks the proliferation and migration of T lymphocytes.

Effects of curcumin on the nervous system

Curcumin directly binds to small beta-amyloids and prevents the accumulation and formation of fibrils in vivo and in vitro. This information indicates that a small amount of curcumin effectively prevents the accumulation of beta-amyloids and their fibril formation and oligomerization which can be the cause of its effect on Alzheimer's disease (10). The curcumin usage inhibits the expression of mRNA of the whole family of amyloid precursor proteins that are stimulated by retinoic acid, and also curcumin causes the return of neurotic changes without changing the cellular life. Manganese curcumin and diacetyl curcumin compounds have a neuroprotective effect, which makes them suitable for use in acute brain pathologies that are related to toxicity caused by NO and oxidant stress, including epilepsy, brain trauma, and stroke (50-52).

Curcumin has an anti-depressant impact in vivo, which can be partly due to the inhibition of monoamine oxidase inhibitors (MAOIs) in the brain of rats (53). It has been stated that hypoacetylation has an important function in the differentiation of stem cells and the expression of several genes. Considering that curcumin as a non-toxic substance is a histone hypoacetylation inhibitor, it can be a new window into a better understanding of the effect of histone hypoacetylation inhibitors in cancer and differentiation of brain stem cells and therapy of central nervous system diseases (54, 55). Also, curcumin can have a protective effect against colchicine-induced cognitive impairment in rats by reduction of lipid peroxidation, correcting the levels of reduced glutathione, and activity of acetylcholinesterase (56).

Effect of curcumin on lipid level

Curcumin truly reduces the level of LDL and VLDL in plasma and causes a decrease in the total level of the liver cholesterol along with an elevation in α-tocopherol in plasma, which indicates the possibility of a relationship between curcumin and alpha-tocopherol in vivo that it can increase the availability of vitamin E and reduce the levels of cholesterol. Prescribing curcumin and its analogs to rats exposed to nicotine greatly reduces the level of plasma lipid, and as a result, this substance has a hypolipidemic effect against the pulmonary toxicity caused by nicotine and can be used as a treatment for hyperlipidemia and atherosclerosis (57, 58). Treatment with curcumin increases 7 folds in mRNA concentration related to LDL receptor, while only a moderate increase in mRNA related to genes coding for sterol production enzymes, HMG-COA reductase enzyme and farnesyl diphosphate also occurs in high concentrations that initiate cellular toxicity (59).

The amount of TG, phospholipid and free fatty acids significantly in alcohol consumption increases, which decreases to a significant extent in people treated with curcuminoids. In a 6-month study in humans, consumption of two different doses of 4 g/d and 1 g/d of curcumin significantly did not change HDL, LDL, and TG. Curcumin inhibits the accumulation of cholesterol due to ox-LDL in cultured rat vascular smooth muscle cells. This compound inhibits angiogenesis in adipose tissue, which, along with its influence on fat metabolism in adipocyte cells, can reduce body fat and be considered as a medicine to prevent obesity (60-62).

Conclusion

Although man moves towards technology more and more every day, he still looks for a way out of many of his problems in nature. Human today has taken help from nature to find new medicinal substances, and the desire and effort to discover new herbal compounds and substances extracted from plants for use in various therapeutic fields has expanded. Every day, new herbal medicines and substances are extracted from plants and have been able to be used in many fields along with chemical medicines and even instead of them. The superiority of these types of compounds over chemical drugs is because they not only have medicinal properties in various fields but also have nutritional properties and vitamins needed by the body. Due to their structural similarity to body molecules, these compounds have fewer side effects. However, due to the presence of various compounds and substances in these plant derivatives, predicting their specific effect is difficult and requires a lot of research. One of these plant materials is turmeric. This yellow powder, which has been used as a nutritional additive in Southeast Asia for years, has also many uses in the field of medicine. Studies in the field of identifying its active components have led to the identification of curcumin, which is one of its active ingredients. Although this substance constitutes a small percentage of turmeric, it has wide therapeutic effects. This combination can have antioxidant, anti-inflammatory, anti-tumor, etc. effects. According to the mentioned properties, curcumin promises a successful herbal therapy approach in the near future.

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