Curcumin's antineoplastic, radiosensitizing and radioprotective properties

Antineoplastické, radiosenzibilizující a radioprotektivní vlastnosti kurkuminu

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Summary

Background: Curcumin is an ingredient in the turmeric plant that gives yellow color to dishes and is used as a spice. It has been used locally/topically and systemically in the treatment of diseases in Far Eastern societies, especially in Indian and Chinese traditional medicine. Curcumin is a natural substance that does not show toxic properties in overdose. In addition to its anti-inflammatory, anti-oxidant, anti-neoplastic, anti-viral, anti-microbial, anti-angiogenic properties, platelet aggregation, apoptosis, and wound healing have been demonstrated in different studies. In recent years, it has been used as a radiosensitizing agent and a radioprotector in radiation therapy. Although curcumin has low bioavailability, it seems to be the ideal molecule due to its low molecular weight, high activity in inhibiting the growth of tumor cells and protecting normal tissues from the side effects of radiation. ***Purpose:*** Curcumin in combination with radiotherapy was discussed in the light of the literature.

Key words

curcumin – radiotherapy – radiosensitizing agent– radioprotector

Souhrn

Východiska: Kurkumin je látka z kořene kurkumy, která dává pokrmům žlutou barvu a používá se jako koření. V kulturách Dálného východu, zejména v indické a čínské tradiční mediccíně, se používá lokálně/místně i systémově při léčbě nemocí. Kurkumin je přírodní látka, která při předávkování nemá toxické účinky. V různých studiích byly prokázány jeho protizánětlivé, antioxidační, antineoplastický, antivirové, antimikrobiální a antiangiogenní účinky a také vliv na migraci buněk, buněčný cyklus, srážení krevních destiček, apoptózu a hojení ran. V posledních letech se kurkumin používá při radioterapii jako radiosenzibilizátor a radioprotektivum. Ačkoli má nízkou biologickou dostupnost, díky své nízké molekulové hmotnosti a vysoké aktivitě inhibovat růst nádorových buněk a chránit zdravé tkáně před nežádoucími účinky radiace se jeví jako ideální molekula. ***Cíl:*** V článku je diskutováno použití kurkuminu v kombinaci s radioterapií z pohledu literatury.

Klíčová slova

kurkumin – radioterapie – radiosenzibilizátor – radioprotektivum

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Introduction

According to the statements of the World Health Organization, 13% of all deaths are due to cancer. It is estimated that this ratio will be 45% in 2030 [1]. It is one of the most studied topics on the prevention and treatment of cancer, due to the high prevalence and incidence of cancer among the causes of death. In recent years, the use of plant extracts in cancer treatment has been increasing day by day. One of these plant extracts is curcumin [2-4].

Curcumin is extracted from the roots of the turmeric plant. It is often used as a food color or spice. It grows in many Asian countries, especially in India and China [4]. Oral bioavailability of curcumin is quite low [5]. The antioxidant, anticancer, anti-inflammatory and antiseptic properties of curcumin are known [5–10]. In recent years, many studies have been carried out on the use of extracts of curcumin plant as a radiosensitizing agent and a radioprotector combined with radiotherapy and promising results have been shown.

In this review, the data regarding the use of curcumin, one of the complementary treatment methods, in combination with radiotherapy were discussed in the light of the literature.

Curcumin (*Curcuma longa*)

Curcumin is herbaceous perennial plant belonging to the ginger family, additionally known as turmeric and Indian saffron. Since the use of turmeric has been found to be effective as a therapeutic agent for various diseases, it has become more popular. Its homeland is South Asia. Although its main producer is India, it is also grown in Bangladesh, China, Indonesia, the Caribbean islands and several countries in South America. It is used as a coloring, preservative and aromatic herb in the food industry. It is also consumed as tea in various regions of Japan [2,3,6,9].

Curcumin is present at 3–5% in turmeric root and is the main ingredient responsible for biological activity. Curcumin, a natural yellow pigment in turmeric, is extracted from the plant's tubers. Four types of curcuminoids are obtained from turmeric roots. These are curcumin, demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin. However, curcumin has the most effective properties compared to the other three types [11]. While curcumin cannot be dissolved in water and ether, it is soluble in ethanol, chloroform, dichloromethane and acetone [6,9].

Usage, bioavailability, dosage and metabolism

A total of 40–85% of orally administered curcumin passes into the gastrointestinal system unchanged and is metabolized in the liver. Most of the curcumin is excreted in stool and a small part in urine [12]. In a study conducted, it was reported that one hour after oral administration of curcumin (1g/kg), curcumin was found in the intestine at a high rate, in smaller amounts in the spleen, liver and kidney, and the lowest in the brain tissue [13]. In a study conducted in rats, it was shown that curcumin given orally was absorbed at a rate of 60% and the remaining part was excreted with stool and urine [14]. In the study conducted, it was reported that an individual of approximately 60 kg could safely take 60–100 mg of curcumin per day [15]. In study conducted by the Department of Prevention of the American National Cancer Institute, no side effects were reported in various experimental animals at doses up to 3.5 g/kg for more than three months [10]. Curcumin has been reported to have no toxic effect even when taken in high doses [3,6,9].

Curcumin, which has a very limited solubility in water ($P < 0.005$), has a very low bioavailability due to its hydrophobic structure [16]. Many studies on increasing the bioavailability have been done. Curcumin and piperine were used as adjuvants in a study conducted in rats. They reported that piperine decreased curcumin elimination half-life and increased curcumin level in plasma 2–4 times [17].

Use of curcumin in medicine

Many effects of curcumin in its use in medicine have been studied. It is known to have antimicrobial, anti-oxidant, anti-inflammatory, antiaging, wound healing, immunomodulating, anticarcinogenic, antimetastatic, neuroprotective, and angiogenesis inhibiting effects [5–7,9–15]. Its antiviral, antimalarial, antifungal, and anti-protozoal (*Leishmania major*) effects have also been reported [18]. Different studies have shown that curcumin reduces the level of cholesterol in the blood, prevents HIV replication, suppresses the symptoms of diseases such as type 2 diabetes, rheumatoid arthritis, multiple sclerosis and Alzheimer's disease, accelerates wound healing, increases bile secretion and prevents liver damage [19]. When the chemical structure of curcumin is analyzed, hydroxyl groups connected to phenyl rings in its structure are responsible for the antioxidant activity of curcumin, while ketone groups and double bonds in its structure are responsible for anti-inflammatory, anticancer and antimutagenic activities. It is thought that curcumin shows its antioxidant activity by affecting enzymes, such as superoxide dismutase, chloramphenicol acetyltransferase and glutathione peroxidase. This gives curcumin the property of being a very powerful and effective natural antioxidant [20]. In addition, curcumin decreases oxidative stress by inactivating the nuclear factor-κB (NK-κB) pathway [21]. Indeed, when curcumin is administered to mice, it has been observed that phagocytic activities of Kupffer cells decrease [22]. Reyes et al reported that curcumin inhibits the increase of cytokines, such as TNF-α, IL-6 and IL-1 [21].

Antineoplastic, radiosensitizing and radioprotective properties of curcumin

Curcumin is a molecule that has been researched much in recent years for its anticancer effects, and there are many articles revealing its antineoplastic mechanism. It has been determined by in vivo and in vitro studies that it shows its inhibitory effect in all three steps of carcinogenesis. These steps are as follows; tumor development, angiogenesis, and tumor growth. It performs its anticancer activity by causing apoptosis in cancerous cells without damaging healthy cells. It also acts by stopping the division of curcumin in some types of cancer cells and increasing cancer cells

the death rate [5,7,23]. Curcumin suppresses the proliferation of mitogen-stimulated blood mononuclear cells and inhibits neutrophil activation [24]. In another study, it was reported that curcumin decreases angiogenesis via nuclear factor kappa B (NF-κB), which is a transcription factor [25]. In addition, curcumin has been reported to have an anti-carcinogenic effect by affecting processes such as inflammation, cell proliferation, some oncogenes, tumor implantation and biotransformation of carcinogens, and inhibition of the transcription factor NF-κB and COX2 enzyme [13,25]. It has been stated that curcumin is an alternative anti-cancer agent that inhibits proliferation by triggering the G1 cell cycle phase regulated by Cdk-2 and that functions as target-specific [26].

Since curcumin has anti-neoplastic activity, low molecular weight and no toxicity, the number of studies on this subject has increased in recent years and has caused it to be tested on different cancer models. Many preclinical in vivo and in vitro studies evaluated as dose dependent have been conducted and it has a protective effect against tumors. It has been shown especially in cancers of the skin, breast, mouth, esophagus, stomach, intestine, colon, lung and liver [27]. Especially obtaining different responses as a result of studies with different cell lines for each cancer type is essential in terms of understanding the pathways curcumin follows when it shows these effects. Abuelba et al reported in their study on breast cancer cell cultures that curcumin suppressed tumor cell growth and increased apoptosis [28]. In the Lopez study, it was reported that curcumin (at a dose of 20 µg/mL) in K-562 human chronic myelocytic leukemia cells stopped tumor growth by 50% [29]. Zunino et al studied four different doses (5, 10, 25, 50 mg/kg) of oral and parenteral curcumin in lymphoblastic leukemia. They found the dose of curcumin 25 mg/kg effective in leukemia [30]. In the study conducted by Prasad et al on breast cancer cell lines, it was stated that curcumin has increased antiproliferative and apoptotic activity depending on dose and time. While this activity decreases the expression level of NF-κB, β-catenin, cyclin D1 and Bcl-2; It has been reported to increase p53, p21 and BAX expression levels [31]. Menon et al, on the other hand, observed that oral administration of 200 nmol/kg of curcumin to or in mice developing melanoma reduced lung metastasis by 80% and increased survival by almost 144% [32].

Clinical studies have started because of the positive results of curcumin during the experimental phase. The first phase I study was conducted by Cheng et al in 2001 in a group of 25 patients with different types of cancer. It was determined that curcumin given to patients at a dose of 8 mg/day for 3 months did not have a toxic effect [33]. In a phase II study conducted by Dhillon et al, daily oral 8 mg curcumin was given to patients with locally advanced pancreatic cancer. It has been reported that curcumin-related toxicity is not observed, it is well tolerated and has strong biological effects [34].

Recent studies indicate that curcumin is effective and safe when used in combination with radiotherapy, as well as its use as an alternative treatment option. It shows this effect by having a double effect on both cancer and normal cells. It increases the genes responsible for apoptosis in cancer cells, making these cells sensitive to radiation. In normal cells, it acts by decreasing oxidative stress and inhibiting the transcription of genes involved in inflammatory response. In addition, curcumin has an effect on cellular antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione transferase) in irradiated systems. It helps its radioprotective activity in increasing glutathione and sulfhydryl groups and decreasing lipid peroxidation. In addition, curcumin prevents side effects due to radiation by inhibiting protein kinase-c, mitogen activating kinases and nitric oxide. Due to these properties, it is a good free radical scavenger and hydrogen donor. In addition, curcumin does not delay cell division and does not alter the division process of the proliferating cell. The growth inhibition is dose-dependent and is reversible with the removal of curcumin, curcumin does not have a toxic effect on the cell [36-41].

Studies examining the radioprotective effects of curcumin extract at different doses have been conducted. Thresiamma et al reported that curcumin (200 µmol/kg) administered orally in rats greatly reduced lipid peroxidation products and collagen hydroxyproline increased by irradiation in serum and liver tissue in lung fibrosis caused by whole body irradiation [42]. Inano and Onoda found that the rate of breast tumor formation in rats fed with a normal diet and exposed to X-rays was 70.3%, whereas in rats where curcumin was added to their diet at 1% and was exposed to X-rays, this rate decreased to 18.5% [43]. In their study in prostate cancer cell series, Chendil et al observed that curcumin at concentrations of 2 and 4 µM significantly increased apoptosis and clonogenic inhibition due to radiation when combined with radiation [44]. In the study evaluated by Hejazi et al, it was stated during the treatment in patients with prostate cancer who received radiotherapy that the antioxidant capacity was higher in the group receiving curcumin [36]. In a multicenter, randomized, double-blind, placebo-controlled study conducted by Wolf et al, they looked at the effect of curcumin applied during radiotherapy on radiation dermatitis in 686 breast cancer patients. As a result, they reported that curcumin did not reduce radiation dermatitis severity [39]. In the review written by Farhood et al, inflammation caused by radiotherapy was seen to be dermatitis, mucositis, fibrosis, pneumonia and bone marrow toxicity in the acute period. They stated that in the chronic period, it may lead to the development of a second cancer. It has been stated that curcumin prevents acute toxicity during radiotherapy due to its anti-inflammatory effect. Again, in this review, it was emphasized that NF-κB can also reduce angiogenesis, tumor growth and metastasis through modulation of the downstream signaling cascade [5]. In another review, the efficacy and safety of curcumin in eliminating resistance was evaluated, since gynecological tumors were resistant to chemotherapy and radiotherapy. It has been empha-

sized that curcumin increases chemosensitization and radiosensitization when it is used with cisplatin, paclitaxel and irradiation in gynecological cancers [40]. In another article examining the effect of curcumin in glioblastoma multiforme, it was stated that a synergistic response was observed when used in combination with both chemotherapy and radiotherapy. However, it has been reported that clinical studies on this subject are insufficient [23]. In the analysis of the studies, it was emphasized that curcumin has both a radiosensitizing and a radioprotective effect. It has been shown to increase radiosensitivity especially in pediatric, lymphoma, sarcoma, prostate, gynecological, pancreatic, liver, colorectal, breast, lung, head/neck and glioma tumors. Although there are few clinical studies performed, it has been reported that there is a radioprotective effect in dermatitis, pneumonia, cataractogenesis, neurocognition, myelosuppression, secondary malignancies and mucositis/enteritis [35].

Conclusion

Curcumin is used as a coloring agent in diets, food and textiles as well as many different pharmacological activities and biological benefits have attracted considerable attention in recent years. Publications on the radioprotector and anticarcinogenic properties of curcumin have begun, and the results seem to be positive. However, enough evidence has yet been obtained for the clinical use of such an effective molecule. The reason for this is that curcumin is rapidly metabolized, its bioavailability is low, the response is different in each type of cancer, the response changes according to the stage of the cancer, and the genetic makeup of the patients is different. Further studies are needed to reveal the molecular effects of curcumin on different organs and metabolic pathways to better understand the effects of curcumin on the human body.

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