Role of Curcumin: A Suppressor of NF-κB Activity in Hepatocellular Carcinoma

33

Saipriya Lammata, Mundla Srilatha, and Ganji Purnachandra Nagaraju

Abstract

Leading as the third cause of cancer-related deaths in the world, hepatocellular carcinoma (HCC) is an aggressive cancer that offers little to no treatment for patients in the advanced stages due to the frequency of recurrence. Moreover, the upregulation of the nuclear factor-kappaB (NF-κB) signaling pathway leads to uncontrolled cell growth, metastasis, and resistance in HCC. Curcumin, a polyphenol derived from turmeric, has been found to inhibit NF-κB activity in HCC and to present other antitumor properties such as anti-proliferation, anti-inflammation, and anti-angiogenic properties. Furthermore, curcumin also acts as a collaborative agent with available chemotherapy and radiotherapy. Working against the drawbacks of poor bioavailability and rapid metabolism, researchers are discovering new ways of encapsulating curcumin in order to exhibit its full efficacy against HCC metastasis.

Keywords

Curcumin · NF-κB pathway · Hepatocellular carcinoma · Angiogenesis · Chemotherapy

The original version of this chapter was revised. The book was inadvertently published without Abstracts and Keywords, which are now included in all the chapters. An erratum to this chapter can be found at https://doi.org/10.1007/978-981-10-6728-0_39

S. Lammata
Rice University, Houston, TX, USA
e-mail: sll9@rice.edu

M. Srilatha
Department of Biotechnology, Sri Venkateswara University, Tirupati, Andhra Pradesh, India
e-mail: sreelathabio@gmail.com

G. P. Nagaraju (✉)
Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA
e-mail: pganji@emory.edu

G. P. Nagaraju, P. V. Bramhachari (eds.), *Role of Transcription Factors in Gastrointestinal Malignancies*, https://doi.org/10.1007/978-981-10-6728-0_33

Abbreviations

Akt	Protein kinase B
bFGF	Basic fibroblast growth factors
COX-2	Cyclooxygenase-2
FLHCC	Fibrolamellar hepatocellular carcinoma
HBx	Protein X of the hepatitis B virus
HCC	Hepatocellular Carcinoma
HHC	Hexahydrocurcumin
IκBs	Inhibitors of NF-κB
IKK	IκB kinase
NF-κB	Nuclear Factor-kappaB
PCD	Programmed cell death
PEI	Percutaneous ethanol injection
PPAR-γ	Peroxisome proliferator-activated receptor-γ
THC	Tetrahydrocurcumin
VEGF	Vascular endothelial growth factor

33.1 Introduction

Caused by either hepatitis B or C, hepatocellular carcinoma (HCC) is a type of liver cancer that stands as the third most common cause of cancer-related deaths in the world [32]. Most cases of HCC range from less than ten patients per 100,000 people in North America and Europe to between 50 and 150 cases per 100,000 people in Asia and Africa [9]. When it comes to the treatment of HCC, surgical resection or liver transplant still stands as the primary approach for most optimal cases of patients in the initial stages of liver cancer [11]. Both resection and transplantation allow patients in the early phases of HCC to preserve any remaining liver functionality. Nonsurgical methods such as percutaneous ethanol injection (PEI), hormonal therapy, and systemic chemotherapy also serve as treatment options [33]. These treatment approaches seek to prevent the progression and any metastatic migration of HCC. Despite the aforementioned treatment methods, HCC patients who are diagnosed at later or advanced stages of the cancer have no hope for impactful treatment [10].

HCC progression and metastasis can occur due to the several signaling pathways at the molecular level. For instance, the nuclear factor-kappaB (NF-κB) pathway (a set of transcription factors) has been known to induce tumor promotion in hepatocytes [26]. In this pathway, NF-κB proteins—p50, p52, c-Rel, RelB, and p65—are retained in the cytoplasm of the cell by inhibitors of NF-κB (IκBs) until the pathway receives an appropriate stimulus, which triggers the ubiquitination of the IκBs and induces the translocation of these proteins into the nucleus [6]. When these proteins accumulate in the nucleus of a hepatocyte, the cell undergoes specific expression of certain genes. These genes that are involved in cell growth control, immune, and inflammatory responses eventually lead to oncogenesis [6]. When NF-κB was

inactivated in later stages of cancer, it was found that tumor growth was suppressed; therefore, drugs that target signaling pathways such as NF-κB could serve as efficient therapeutic approaches to the treatment of HCC [29]. Inhibition of the NF-κB pathway should be the focus of research as targeting molecular pathways can prompt the emergence of treatment that serves patients in the advanced stages of HCC.

Many investigations have chosen to look toward more natural agents in order to prevent the progression of tumors in several cancer malignancies. Inhibitors of NF-κB include the natural agent, curcumin, which exhibits anti-inflammatory, anti-necrotic, and anti-cancerous properties [26]. Curcumin is the primary polyphenol found in turmeric, an Asian herb that has been used for medicinal purposes since ancient times [31]. Throughout the decades, curcumin has been utilized by numerous civilizations as it exhibits pro-health qualities against diseases and tumorous characteristics. For instance, in the field of cancer, curcumin works with several genes and proteins—vascular endothelial growth factor (VEGF), cyclin D1, NF-κB, cyclooxygenase-2 (COX-2), and more—in order to reduce the progression of tumor growth in carcinogenesis [31]. Despite its salubrious nature, curcumin in the human body retains a low bioavailability and poor absorption [18]. Thus, many clinical trials involving curcumin are still undergoing as higher dosages of the compound are contemplated and researched.

33.2 Structure of Curcumin

Turmeric comprises of three primary curcuminoids in the following order from most to least: curcumin, demethoxycurcumin, and bisdemethoxycurcumin [39]. The structure of curcumin consists of the combination of methoxy groups on the phenyl rings [31]. Although this specific structure allows curcumin to exhibit anti-inflammatory and antioxidant qualities, it also prevents the stability of the compound in aqueous solutions, such as water, except for highly acidic solvents [7, 31]. In addition to highly acidic conditions, curcumin was also found to have dissolved in organic solutions under the presence of light, resulting in the photodegradation of the compound [40]. Lowering the pH of the solvent retained the chemical stability of curcumin. The compound's instability can be specifically attributed to a B-diketone moiety in the molecule's diene structure, and deletion of this group can lead to a potential stabilized structure of curcumin [23, 43]. Therefore, modification of the structure of curcumin permits researchers to incorporate the molecule into treatment of the HCC via regular physiological conditions of the human body.

Not only does curcumin exhibit chemical instability in neutral or physiological conditions, but the natural agent also presents poor bioavailability. The human body absorbs curcumin at a low rate due to several factors: the placement of bodily tissues, a decrease in plasma, and an elevation in metabolism [36]. Experiments containing high dosages of curcumin—about 400 mg—only demonstrated 60% absorption in a rat model, and researchers found a large portion of curcumin exiting the body via feces, aligning with the discovery of most of the curcumin in the large intestine [36]. In addition to the large intestine, metabolized curcumin was also

found in the liver [30]. Fortunately, heating curcumin increased its solubility in neutral aqueous solutions and did not destroy its biological identity [21]. Furthermore, the administration of curcumin is also significant in the resulting level of bioavailability; for instance, nasal and intravenous administration of curcumin was followed by higher levels of absorption in rat-based model as compared to that of an oral administration of the natural compound [30]. A low concentration of curcumin in the body prevents its full efficacy in the treatment of cancers such as HCC, often pushing research to implement either greater doses, ways to increase solubility, or modified versions of the golden compound.

A significant factor behind its poor bioavailability is curcumin's rapid metabolism. Research has found curcumin to remain in the body after ingestion, primarily in three locations: the liver, intestine, and kidney [17, 41]. These tissues have a high rate of metabolism, and this aspect coupled with the body's eradication of the natural compound results in low concentrations of curcumin in the body after treatment [41]. The amount of curcumin used in treatment—whether a high or low dosage—did not carry much significance because the compound quickly metabolized after ingestion [41]. In the body, however, curcumin metabolites include curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin (THC), and hexahydrocurcumin (HHC) via catalysis by enzymes located in the cytosol and microsomes [17]. Several investigations have found traces of the aforementioned metabolites in the liver and intestine. Some metabolites were found to have the same salubrious properties as curcumin itself [17]. Although curcumin and its metabolites exhibit antitumor properties, the delivery as a treatment approach has pushed researchers to investigate other forms of modification of the natural agent such as curcumin nanoformulation, which has shown a decrease in the necessary dosage and in increase in the efficacy of the treatment [44]. Since the rapid metabolism of curcumin prevents its higher bioavailability in the body, further research is required into investigating the uses of curcumin metabolites and potential modifications—such as nanoparticles and other forms of encapsulation—so that the full efficiency of curcumin can be utilized in HCC treatment.

33.3 The Nuclear Factor-kappaB Pathway in Hepatocellular Carcinoma

The NF-κB pathway, also known as a set of transcription factors, plays an important and progressive role in many cancers, including HCC. The NF-κB pathway drives the metastasis of cancer cells [14]. As stated before, this signaling pathway consists of the following five proteins known as p50, p52, c-Rel, RelB, and p65, and these proteins remain inactive in the cytoplasm [14]. What keeps these proteins is the cytoplasm are molecules known as IκBs, another set of proteins that latches onto the domains of the aforementioned NF-κB proteins [14]. When activated by stimuli or signal cascades, the IκBs result in ubiquitination and start to degrade [45]. Stimuli that active the pathway include stress promoters and cytokines associated with an inflammation response [6]. When the IκBs start to degrade due to the activation of the NF-κB pathway, the translocation of the NF-κB proteins, which have dimerized

at this point, into the nucleus results in gene expression and responses: inflammation, cell growth, and ultimately the progression of cancer [27, 45]. The activation of the NF-κB pathway ends in the binding of the DNA in the nucleus and the upregulation of genes associated with inflammatory responses and apoptotic properties, which aid in the progression and metastasis of cancer cells [6]. The goal of suspending and preventing further metastasis and progression of HCC can give researchers a specific pathway to target in hopes of creating a therapeutic approach with a drug that inactivates NF-κB.

Not only does the activation of the NF-κB pathway result in gene expression of cancerous properties, but it also results in the stimulation of other NF-κB subunits [6]. Within the NF-κB signaling pathway exists two specific pathways: canonical and noncanonical [27]; the IκB kinase (IKK) and its two components, IKKalpha and IKKbeta, comprise the canonical NF-κB pathway as these molecular aspects of the pathway result in the ubiquitination and degradation of the IκBs [35]; on the other hand, the phosphorylation of p100 results in the translocation of the p52/RelB complex into the nucleus [38]. Despite either the canonical or noncanonical pathway, the NF-κB signaling cascade nonetheless plays a stimulating role in the progression of HCC tumorigenesis. For instance, Wang et al. [42] found that protein X of the hepatitis B virus (HBx) plays a potential role in the activation of the NF-κB pathway, leading to the promotion of tumor growth in cases of HCC. Furthermore, this investigation went on to find that a positive correlation existed between the amount of HBx and the amount of a NF-κB transcription factor known as p65, showing that HBx may indeed influence the activation of the NF-κB pathway [42]. Another investigation involving the technique of immunostaining and fibrolamellar hepatocellular carcinoma (FLHCC) tissue samples revealed that there were amounts of the NF-κB protein p65 found in FLHCC tissues as compared to little or none of the protein's presence in normal tissue [22]. A sharp contrast exists between the expression levels of NF-κB proteins in tumorous liver tissue as compared to the lack of the NF-κB pathway's influence in normal tissue; this shows that the NF-κB signaling pathway definitely plays a role in the progression of HCC tumorigenesis as its presence marks an identification between cancerous and noncancerous tissue.

In tumorous tissue, NF-κB tends to express levels of inflammation and promotes cell growth to advance HCC tumorigenesis. The NF-κB pathway was found to have a heavy influence in the control of apoptosis or an amplified form of programmed cell death (PCD), which stands as an essential factor in the promotion of tumorigenesis in HCC [12]. High levels of the activation of the NF-κB pathway were found in carcinoma tissues as the pathway promoted cell proliferation in vitro by preventing apoptotic expression [19]. Although the NF-κB signaling pathway may play other beneficial roles in the immune system, the translocation of NF-κB proteins into the nucleus leads to a dysregulation that advances tumorigenesis [19]. The versatile uses of the NF-κB pathway have led researchers to determine a way to prevent the promotion of tumorigenesis but retain the continuation of other immune responses for the benefit of other bodily systems [19]. The NF-κB pathway has several functions—advantageous and disadvantageous—in the human body's immune system; this objective leads to the development of an exclusive drug in HCC treatment with

the goal to regulate a multifarious signaling cascade by preventing the HCC cell proliferation and metastasis.

33.4 Curcumin and the Nuclear Factor-kappaB Pathway in Hepatocellular Carcinoma

Research has found the natural golden agent of curcumin as a mechanism of the NF-κB pathway's inactivation. The NF-κB signaling pathway is present in numerous cancers as the pathway silences apoptotic activity [20]. Curcumin has been found to suppress the NF-κB pathway and its subunits and to increase apoptotic results in HCC cell lines by depending on the mediation of caspase-3, caspase-8, caspase-9, or other molecules [28]. In addition to the suppression of the NF-κB pathway, curcumin also suppressed the expression levels of COX-2, which appears in other cancers and diseases; furthermore, curcumin also reduced the expression of cytokines associated with an inflammatory response [18]. Liver inflammation has been designated as a marker of HCC progression in the initial stages, and the use of curcumin has reduced expression levels of HCC indicators, such as the VEGFs and oxidative stress [1]. Not only does curcumin have apoptotic and anti-inflammatory qualities, but the natural compound has also led to the designation of markers in HCC progression by identifying the receptors that promote the progression of HCC.

In addition to apoptotic and anti-inflammatory action, curcumin also decreases levels of cell proliferation. For instance, by decreasing the expression levels of cyclin D1 and the Wnt/beta-catenin signaling pathway, curcumin has restrained the growth of HCC tumors and cell proliferation [20]. The beta-catenin signaling pathway regulates the expression of cell proliferation in numerous cancers and targets the protein known as cyclin D1 of which an increase can induce cell multiplication due to an uncontrolled cell cycle [37, 46]. An addition, however, must be made to the aforementioned statements; not only does curcumin exhibit anti-proliferative properties by inhibiting the Wnt/beta-catenin signaling pathway and cyclin D1, but the natural agent does the same job by activating a molecule known as peroxisome proliferator-activated receptor-γ (PPAR-γ). Through deactivation of the NF-κB pathway, the PPAR-γ molecule reduces inflammation and cell proliferation; in vivo models revealed that an increase in the expression levels of PPAR-γ occurred in the presence of curcumin [24]. The reduction of anti-apoptotic genes also decreased cell proliferation in several cancer cell lines, and curcumin had an impactful influence in this decline [34]. Overall, curcumin's targets are molecules or pathways that increase cancer cell amplification; therefore, by allowing curcumin to enter the body and inhibit these proliferative molecular structures, cancer cell proliferation ceases to continue.

Another factor that promotes tumorigenesis is the formation of new blood vessels, known as angiogenesis, which can be combatted by curcumin as this natural agent retains anti-angiogenic properties in addition to its aforementioned qualities: anti-inflammatory, anti-proliferative, and anti-apoptotic. Angiogenesis is the growth of new blood vessels from existing channels, and this formation aids in the

promotion of tumors [25]. Angiogenesis is one of the primary factors of tumor metastasis because it provides two functions: (1) providing nutrients to growing tumors and (2) allowing cancer cells to enter the body circulation [13]. Any dysregulation in oncogenes or tumor suppressor genes can result in the development of angiogenesis and the advancement of tumorigenesis [13]. By reducing the expression levels of proangiogenic receptors such as VEGF, correlated genes, and basic fibroblast growth factors (bFGF), curcumin exhibited anti-angiogenic expression and could prevent the progression of tumor growth [25]. In vivo study revealed a dichotomy of purpose in curcumin: first, the natural compound suppressed the proangiogenic markers to inhibit tumor growth, but curcumin could also inhibit angiogenesis in tumors that already expressed escalated levels of these proangiogenic indicators [5]. The upregulation of such proangiogenic markers—VEGFs, bFGFs, and oncogenes—is essential for tumor growth, yet curcumin suppresses these markers and even inhibits NF-κB activation; furthermore, the natural yellow compound also decreases the expression of cell adhesion molecules, which aid in the migration and metastasis of HCC tumors [8]. By inhibiting angiogenesis in HCC metastasis through the use of curcumin, researchers have been able to prevent the progression of tumorigenesis into advanced stages, where little to no treatment improves the patient's survival rate; rather, the utilization of curcumin offers protection from the advancement of HCC metastasis.

Although curcumin retains properties associated with anti-inflammation, apoptosis, and anti-proliferation, researchers have taken the natural agent found in turmeric and have combined it with the current chemotherapy available to discover new treatment approaches for HCC. For example, a chemo drug known as paclitaxel has shown anti-proliferative effects in the treatment of cancers such as breast and lung; its combination with curcumin, however, shows promising results in HCC treatment [47]. When exhibited on HCC cell lines, the combination of curcumin and paclitaxel showed that the addition of the natural yellow compound enhanced the antitumor properties of the chemo drug, reducing cell proliferation and promoting cell apoptosis [47]. Furthermore, paclitaxel is known to induce other signaling pathways such as the NF-κB and protein kinase B (Akt) pathways, which curcumin suppresses; in this way, the combination of paclitaxel and curcumin allows chemotherapy to continue without any detrimental activations that could impel tumorigenesis [3]. Paclitaxel, however, is not the only chemo drug that has been intertwined with curcumin in HCC treatment; cisplatin and doxorubicin, additional drugs in chemotherapy, have also displayed several benefits when used in combination with curcumin. The integration of curcumin and cisplatin as a treatment approach showed that cells were sensitized to just cisplatin, whereas curcumin and doxorubicin revealed supplementary effects on the cells [28]. Overall, incorporating curcumin with either cisplatin or doxorubicin revealed that NF-κB expression levels were lower than those of a single chemo drug at work [28]. As an instrument of sensitization and efficiency, curcumin enhances the effects of its complementary chemo drug, thus inhibiting the migration and invasion of HCC cells; this combination of curcumin and chemotherapy opens a new door of treatment options that offer a way to terminate, or potentially reduce the uncontrolled growth, HCC metastasis.

Researchers have not only experimented with curcumin and chemotherapy, but they have also taken note of the effects of curcumin on radiotherapy. Radiotherapy is imperfect in HCC treatment because the frequent recurrence of the cancer calls for higher doses of chemo, but this escalation in chemotherapy prevents the patient from fully undergoing irradiation [16]. Curcumin, however, sensitizes targeted cells to radiation and even to the effects of other chemo drugs in vitro and in vivo [4, 16]. In more specificity, curcumin was found to enhance the antitumor effects of radiotherapy by decreasing the expression levels of any NF-κB activity that radiation promoted initially; in this way, curcumin enhances the effects of radiation on the tumors while diminishing the activity of a signaling pathway that promotes tumorous agents [16]. In vivo study reveals that curcumin not only increased the anticancer effects of radiation, but the natural compound also enhanced the antitumor effects of gemcitabine, a known chemo drug, when put into use as a treatment approach [15]. Hatcher et al. [15] also revealed that the activation of the NF-κB pathway occurs due to the radiotherapy, but curcumin inactivates this signaling pathway known for cell growth and other NF-κB subunits. In fact, radiative toxicity relates to an abnormal regulation of the NF-κB signaling pathway, but curcumin protects cells from this damage—known as radioprotection—by inhibiting the proteins that stimulate this toxicity [2]. From its role in fighting cancer, researchers can see that not only does curcumin have anticancer properties, but the natural agent is a collaborative factor; curcumin works in several combinations with radiation and chemotherapy in order to enhance antitumor characteristics and lessen factors of tumor promotion.

33.5 Conclusion and Future Prospectus

HCC is an aggressive cancer that metastasizes very quickly; unfortunately, little to no treatment is available for patients undergoing advanced stages of this form of liver cancer. With the discovery and studies done on curcumin, however, research has allowed the possibility of offering treatment to patients at both initial and advanced stages of HCC. Curcumin, a natural golden compound found in turmeric, promises several salubrious effects: anti-inflammatory, anti-proliferative, and antioxidant. Thus, this yellow agent has made its debut in HCC treatment and leads to a promising future with chemotherapy, radiotherapy, and possibly targeted molecular therapy.

Although curcumin promises many pro-health qualities, the natural agent does have its drawbacks in deliverance. For instance, curcumin exhibits chemical instability in physiological conditions; the solubility of the yellow compound is only limited to highly acidic or organic solvents. Furthermore, curcumin displays poor bioavailability due to its rapid metabolism; in fact, the compound's fast metabolism has revealed that curcumin's metabolites exhibit the same properties as the original agent itself. Faulty deliverance of this natural agent as a therapeutic target is what prevented curcumin from exhibiting its full efficacy in treating HCC tumorigenesis. Thus, further research—such as the ongoing investigations on curcumin

nanoformulation—is required so that proper modifications can be made to condone curcumin's full efficiency.

Curcumin inhibits the NF-κB signaling pathway, also known as a set of transcription factors, in HCC. The translocation of these NF-κB proteins into the nucleus leads to gene expression of inflammation and cell growth of which both exhibit escalated levels in tumorous tissue. By deactivating the NF-κB pathway, curcumin enhances levels of apoptosis and anti-inflammation. Furthermore, the yellow compound also inhibits cyclin D1 and the beta-catenin pathway in accordance to enhancing expression of the PPAR-γ molecule in order to decrease cell proliferation and HCC metastasis. Curcumin does not stop at its anti-proliferative quality for the compound also reveals anti-angiogenic qualities: terminating formation of new blood vessels and inhibiting proangiogenic markers in developed HCC tumors. Lastly, curcumin pairs with chemotherapy and radiotherapy in order to inhibit the induced NF-κB activity and to sensitize cancer cells to the full exposure of the chemo drugs and radiation, which stand as complementary factors to the effects of curcumin. Alas, curcumin allows research to inhibit, or at least hinder, the aggressive nature of HCC metastasis as this golden compound welcomes the scientific community to a range of new treatment approaches that apply to patients at all stages of HCC.

References

1. Afrin R, Arumugam S, Rahman A, Wahed MII, Karuppagounder V, Harima M, Suzuki H, Miyashita S, Suzuki K, Yoneyama H (2017) Curcumin ameliorates liver damage and progression of NASH in NASH-HCC mouse model possibly by modulating HMGB1-NF-κB translocation. Int Immunopharmacol 44:174–182
2. Aggarwal BB, Kumar A, Bharti AC (2003) Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 23(1/A):363–398
3. Amornwachirabodee K, Chiablaem K, Wacharasindhu S, Lirdprapamongkol K, Svasti J, Vchirawongkwin V, Wanichwecharungruang SP (2012) Paclitaxel delivery using carrier made from curcumin derivative: synergism between carrier and the loaded drug for effective cancer treatment. J Pharm Sci 101(10):3779–3786
4. 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(1):133–164
5. Arbiser JL, Klauber N, Rohan R, Van Leeuwen R, Huang M-T, Fisher C, Flynn E, Byers HR (1998) Curcumin is an in vivo inhibitor of angiogenesis. Mol Med 4(6):376
6. Baldwin AS (2001) Control of oncogenesis and cancer therapy resistance by the transcription factor NF-κB. J Clin Invest 107(3):241–246
7. Begum AN, Jones MR, Lim GP, Morihara T, Kim P, Heath DD, Rock CL, Pruitt MA, Yang F, Hudspeth B (2008) Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. J Pharmacol Exp Ther 326(1):196–208
8. Bhandarkar SS, Arbiser JL (2007) Curcumin as an inhibitor of angiogenesis. In: The molecular targets and therapeutic uses of curcumin in health and disease. Springer, Dordrecht, pp 185–195
9. Blum HE (2011) Hepatocellular carcinoma: HCC. Hepat Mon 11(2):69
10. Bruix J, Llovet JM (2002) Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 35(3):519–524

11. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. Hepatology 53(3):1020–1022
12. Bubici C, Papa S, Pham C, Zazzeroni F, Franzoso G (2006) The NF-κB-mediated control of ROS and JNK signaling. Histol Histopathol 21(1):69–80
13. Chintana P (2013) Role of curcumin on tumor angiogenesis in hepatocellular carcinoma. Naresuan Univ J Sci Technol 16(3):239–254
14. Dolcet X, Llobet D, Pallares J, Matias-Guiu X (2005) NF-κB in development and progression of human cancer. Virchows Arch 446(5):475–482
15. Hatcher H, Planalp R, Cho J, Torti F, Torti S (2008) Curcumin: from ancient medicine to current clinical trials. Cell Mol Life Sci 65(11):1631–1652
16. Hsu F-T, Liu Y-C, Liu T-T, Hwang J-J (2015) Curcumin sensitizes hepatocellular carcinoma cells to radiation via suppression of radiation-induced NF-κB activity. Biomed Res Int. 363671–363677
17. Ireson CR, Jones DJ, Orr S, Coughtrie MW, Boocock DJ, Williams ML, Farmer PB, Steward WP, Gescher AJ (2002) Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol Prev Biomark 11(1):105–111
18. Jurenka JS (2009) Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev 14(2)
19. Kojima M, Morisaki T, Sasaki N, Nakano K, Mibu R, Tanaka M, Katano M (2004) Increased nuclear factor-kB activation in human colorectal carcinoma and its correlation with tumor progression. Anticancer Res 24(2B):675–682
20. Kunnumakkara AB, Anand P, Aggarwal BB (2008) Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett 269(2):199–225
21. Kurien BT, Scofield RH (2009) Oral administration of heat-solubilized curcumin for potentially increasing curcumin bioavailability in experimental animals. Int J Cancer 125(8):1992–1993
22. Li W, Tan D, Zenali MJ, Brown RE (2010) Constitutive activation of nuclear factor-kappa B (NF-κB) signaling pathway in fibrolamellar hepatocellular carcinoma. Int J Clin Exp Pathol 3(3):238–243
23. Liang G, Yang S, Zhou H, Shao L, Huang K, Xiao J, Huang Z, Li X (2009) Synthesis, crystal structure and anti-inflammatory properties of curcumin analogues. Eur J Med Chem 44(2):915–919
24. Lv FH, Yin HL, He YQ, Wu HM, Kong J, Chai XY, Zhang SR (2016) Effects of curcumin on the apoptosis of cardiomyocytes and the expression of NF-κB, PPAR-γ and Bcl-2 in rats with myocardial infarction injury. Exp Ther Med 12(6):3877–3884
25. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC (2006) Multiple biological activities of curcumin: a short review. Life Sci 78(18):2081–2087
26. Muriel P (2009) NF-κB in liver diseases: a target for drug therapy. J Appl Toxicol 29(2):91–100
27. Naugler WE, Karin M (2008) NF-κB and cancer—identifying targets and mechanisms. Curr Opin Genet Dev 18(1):19–26
28. Notarbartolo M, Poma P, Perri D, Dusonchet L, Cervello M, D'Alessandro N (2005) Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF-κB activation levels and in IAP gene expression. Cancer Lett 224(1):53–65
29. Paul AG (2005) NF-κB: a novel therapeutic target for cancer. Eukaryon 1(1):2
30. Prasad S, Tyagi AK, Aggarwal BB (2014) Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat: Off J Korean Cancer Assoc 46(1):2–18
31. Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramirez-Tortosa M (2016) Curcumin and health. Molecules 21(3):264
32. Ramesh V, Selvarasu K, Pandian J, Myilsamy S, Shanmugasundaram C, Ganesan K (2016) NFκB activation demarcates a subset of hepatocellular carcinoma patients for targeted therapy. Cell Oncol 39(6):523–536

33. Ryder SD (2003) Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 52(suppl 3):iii1–iii8
34. Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, Limtrakul P, Badmaev V, Aggarwal BB (2007) Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcinogenesis 28(8):1765–1773
35. Senftleben U, Cao Y, Xiao G, Greten FR, Krähn G, Bonizzi G, Chen Y, Hu Y, Fong A, Sun S-C (2001) Activation by IKKα of a second, evolutionary conserved, NF-κB signaling pathway. Science 293(5534):1495–1499
36. Shehzad A, Khan S, Shehzad O, Lee Y (2010) Curcumin therapeutic promises and bioavailability in colorectal cancer. Drugs Today 46(7):523
37. Shtutman M, Zhurinsky J, Simcha I, Albanese C, D'Amico M, Pestell R, Ben-Ze'ev A (1999) The cyclin D1 gene is a target of the β-catenin/LEF-1 pathway. Proc Natl Acad Sci 96(10):5522–5527
38. Sun S-C (2011) Non-canonical NF-κB signaling pathway. Cell Res 21(1):71–85
39. Ting C-T, Li W-C, Chen C-Y, Tsai T-H (2015) Preventive and therapeutic role of traditional Chinese herbal medicine in hepatocellular carcinoma. J Chin Med Assoc 78(3):139–144
40. Tønnesen HH, Karlsen J (1985) Studies on curcumin and curcuminoids. Z Lebensm Unters Forsch 180(5):402–404
41. Wahlström B, Blennow G (1978) A study on the fate of curcumin in the rat. Basic Clin Pharmacol Toxicol 43(2):86–92
42. Wang T, Wang Y, Wu M-C, Guan X-Y, Yin Z-F (2004) Activating mechanism of transcriptor NF-kappaB regulated by hepatitis B virus X protein in hepatocellular carcinoma. World J Gastroenterol 10(3):356–360
43. Wang Y-J, Pan M-H, Cheng A-L, Lin L-I, Ho Y-S, Hsieh C-Y, Lin J-K (1997) Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharm Biomed Anal 15(12):1867–1876
44. Yallapu MM, Jaggi M, Chauhan SC (2012) Curcumin nanoformulations: a future nanomedicine for cancer. Drug Discov Today 17(1):71–80
45. Yamamoto Y, Gaynor RB (2001) Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. J Clin Invest 107(2):135–142
46. Zheng R, Deng Q, Liu Y, Zhao P (2017) Curcumin inhibits gastric carcinoma cell growth and induces apoptosis by suppressing the Wnt/β-catenin signaling pathway. Med Sci Monit 23:163–171
47. Zhou M, Li Z, Han Z, Tian N (2015) Paclitaxel-sensitization enhanced by curcumin involves down-regulation of nuclear factor-κ B and Lin28 in Hep3B cells. J Recept Sig Transduct 35(6):618–625