INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

"REVIEW ON CURCUMIN AS A THERAPEUTIC REMEDY FOR A LIVER CANCER"

Miss. Bhandari Sejal[1], Mr. Kale. A. D[2], Dr. Garje S.Y[3], Dr. Gaffar G. A[4]

[1,2,3,4]SAJVPM'S College Of Pharmaceutical Science And Research Centre, Kada (Beed), Maharashtra, India.

Corresponding Author: Bhandari Sejal

ABSTRACT

Primary liver cancer, also known as hepatocellular carcinoma (HCC), is one of the most lethal cancers having worldwide prevalence. Although most HCC cases are reported in the developing countries of Asia and Africa, there has been an alarming increase in HCC cases in Western Europe as well as United States. Chronic liver diseases, viral hepatitis, alcoholism as well as dietary carcinogens, such as aflatoxins and nitrosoamines, contribute to HCC. Liver transplantation as well as surgical resection at best offer limited treatment options. Thus, there exists a critical need to investigate and evaluate possible alternative chemopreventive and therapeutic strategies which may be effective in the control of liver cancer. HCC, most often, develops and progresses in a milieu of oxidative stress and inflammation. Phytochemicals, such as dietary polyphenols endowed with potent antioxidant as well as anti-inflammatory properties, provide a suitable alternative in affording alleviation of HCC. Curcumin, the principal polyphenolic curcuminoid, obtained from the turmeric rhizome Curcuma longa has long been used to cure several chronic ailments, such as neoplastic and neurodegenerative diseases. Studies suggest that curcumin may have antitumor, antioxidant, and anti-inflammatory properties. This article reviews the effects of curcumin in preclinical in vitro and in vivo models of HCC with particular emphasis to its antioxidant, apoptotic and anti-inflammatory effects as well as involvement in various molecular signaling mechanisms.

1. INTRODUCTION

Curcumin

2.1) Synonyms: Saffron Indian; haldi (Hindi); Curcuma; Rhizoma cur-cumae.

2.2)Biological Source: -Curcumin is the main active ingredient of turmetic, a spice obtained by grinding the dried rhizomes of the plant Curcuma longa.[1]turmeric dry rhizome is composed mainly of starch, having also carbohydrates, proteins, lipids, fiber, curcuminoid pigments, sesquiterpenes (turmerone, atlantone, zingiberone, turmeronol, germacrone, α-curcumene, β-sesquiphellanderene, bisacurone, curcumenone, dehydrocurdione, procurcumadiol, bis-acumol, curcumenols, zedoaronediol, bisabolene, and curlone), and caffeic acid[2,3]The curcuminoid content typically varies between 2% and 9%. Curcumin is the most abundant curcuminoid in turmeric, but traces of its precursors, desmethoxycurcumin and bisdemethoxycurcumin are also present.

2.3 Chemical Constituents: -Turmeric contains about 5 percent flexible oil, amber, a large amount of zingiberaceous starch and yellow substances known as curcuminoids. The main component of curcuminoids is known as curcumin (50 - 60 percent). Chemically, the Curcuma varieties contain hot oils, starch and curcumin. Curcumin and other related curcuminoids such as Demethoxy curcumin and BisDemethoxy curcumin are reported to be responsible for the yellow colour in some species. The oil content varies from 1 - 6.5 percent and is made of mono and sesquiterpene such as A and B pinene, phellandrene, camphor, camphene, DL-ar-turmerone stain and a, ß curcumenes. Types such as C. angustifolia and C. caulina has high starch and is used instead of the root of the arrow.

2. 4 Chemical test:

1) Turmeric powder on treatment with concentrated sulphuric acid forms red Colour.

2) On addition of alkali solution to turmeric powder red to violet colour is produced.

3) With acetic anhydride and concertrated sulphuric acid turmeric gives violet colour. Under UV light this colour is seen as an intense red fluorescence.

4) A paper containing turmeric extract produces a green colour with borax solution.

5) On addition to boric acid a reddish-brown colour is formed which, on addition of alkalies, changes to greenish-blue.

2.5 Chemistry of curcumin-Curcumin has the chemical formula $C_{21}H_{20}O_6$.It is also refered to as diferuloylmethane, having a very long IUPAC denomination: (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5dione.

Itschemical structure comprises two aromatic ring systems with o-methoxy phenol groups connected by a seven-carbon linker consisting of anα, β-unsaturated β-diketone moiety that exhibits keto-enol tautomerism in solution.[4]

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

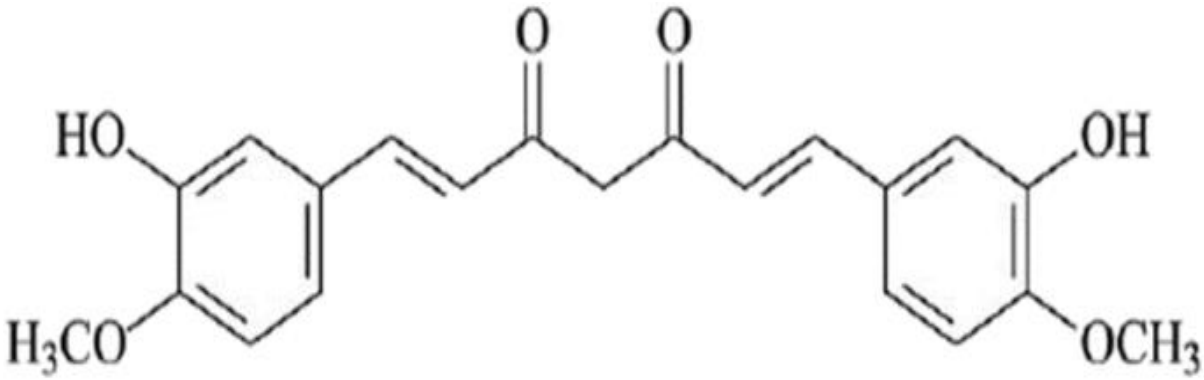
www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

Due to extended conjugation, the π electron cloud is distributed all along the molecule making curcumin very hydrophobic, with a log p value of 3.38 and an extremely low solubility in water (1.34 ± 0.02 mg/L).[5] Curcumin is reasonably stable in water at pH < 7.0 due to structural stabilization by the conjugated diene; in PBS and at pH > 8 it may degrade rapidly (10 min). In fact, curcumin possesses three ionizable protons with pKa values of approximately 8.5 (enolic proton) and 10–10.5 (two phenolic protons).[6]

Curcumin absorbs light from the near ultraviolet (around 340 nm) to the indigo-blue spectral region (450–460 nm), with absorption peaking at 410–430 nm (violet light). It presents a fluorescence band between 460 and 560 nm. Furthermore, curcumin is sensitive to ultraviolet radiation and its degradation is accelerated by exposure to sunlight. [7,8]

When irradiated with light above 400 nm, curcumin undergoes a self-sensitized photo-decomposition where singlet oxygen is involved, but when reactive oxygen species are not available, other decomposition mechanisms are triggered. Photodegradation products include vanillin, vanillic acid, 4-vinyl-guaiacol, ferulic aldehyde, and ferulic acid. [9]



Curcumin

2.6 Extraction of Curcumin and detection-The largest worldwide producer of turmeric is India, where it has been used as a home-remedy for several ailments for ages. Depending on its origin and the soil conditions where it is grown, turmeric contains 2%–9% curcuminoids.[55] The word "curcuminoid" indicates a group of compounds such as curcumin, demethoxycurcumin and bis-demethoxycurcumin and cyclic curcumin. Out of these, curcumin is the major component, and cyclic curcumin is the minor component.

Solvent extraction followed by column chromatography has been the most commonly employed method reported. Soxhlet extraction, ultrasonic extraction, microwave, zone-refining and dipping methods have been tried, and among these the Soxhlet, ultrasonic and microwave extractions are the most commonly employed methods. [10]Recently pulse ultrasonic and microwave-assisted extraction methods have also been reported to be better than the continuous methods. Being free from organic solvents, pilot plants based on supercritical carbon dioxide have been established in several countries for the extraction of curcumin from turmeric. There are also a few reports on enzyme-assisted extraction, where pretreatment of turmeric with enzymes like α-amylase and glucoamylase yielded significant increases in curcumin yield.[11]

Curcumin can be separated from curcumin mix (a mixture of curcumin, demethoxycurcumin and bisdemethoxycurcumin) by column chromatography by adsorbing the mixture on silica gel using mixtures of solvents like dichloromethane/acetic acid or methanol/chloroform to yield three different fractions. The curcumin fraction is further purified on silica gel using chloroform/dichloromethane and ethanol/methanol mixtures as eluents Methods for the detection and estimation of curcumin have mostly employed the high performance liquid chromatography (HPLC) technique. In general reverse phase C18 columns are used as stationary phase and different gradients of solvents containing acetonitrile/water or chloroform/methanol have been employed as the mobile phase.[12]

For detection of curcumin, in the wavelength range from 350 to 450 nm range or in the UV region using a common detection wavelength in the range of 250 to 270 nm. Liquid chromatography-coupled mass spectrometry has been another versatile tool for detecting curcumin. Microemulsionelectrokinetic chromatography using oil droplets and surfactants, has been found to be good for both extraction and estimation of curcumin in food and medicinal samples. Capillary electrophoresis with amperometric detection can be routinely employed to estimate curcumin/turmeric in food materials.[13] Ultra-performance liquid chromatography (UPLC) coupled with online tandem mass spectrometry has been used to detect curcumin metabolites in plasma and urine, with detection limits of 2.5 ng/mL[14]

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

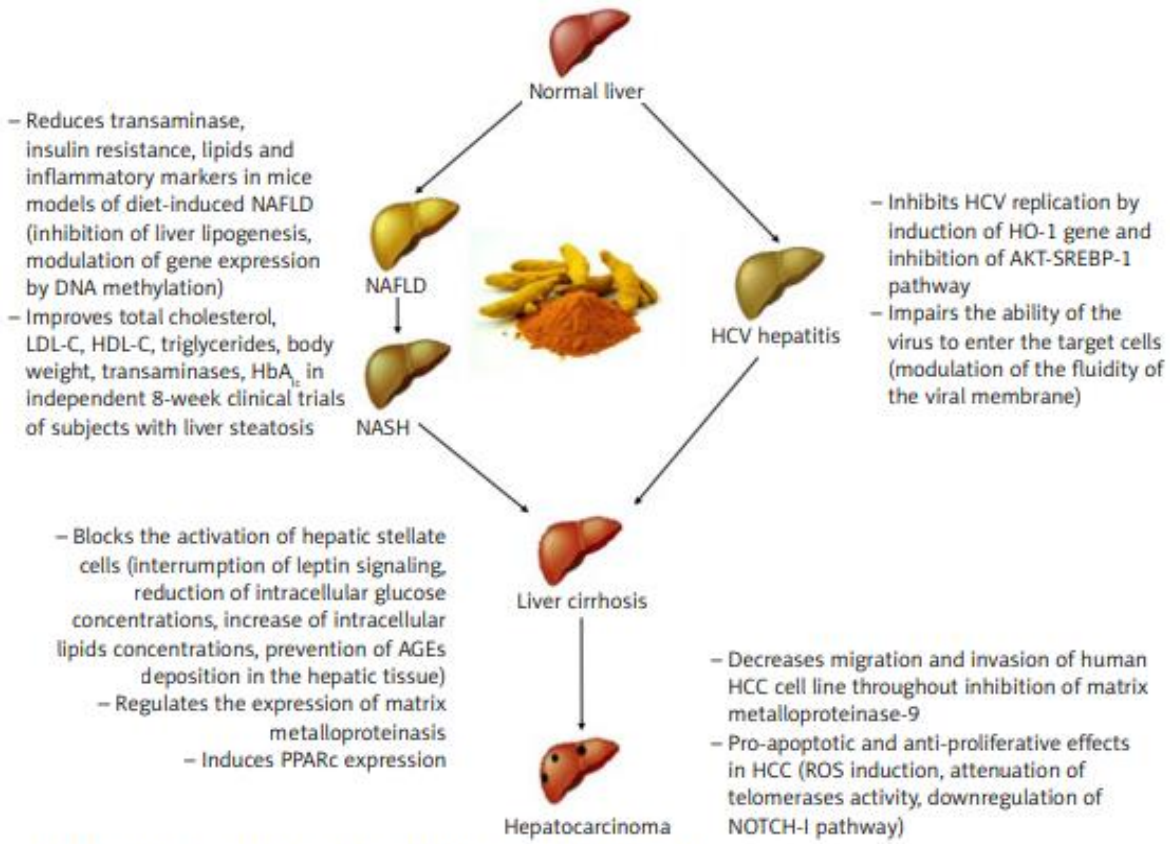


Figure 1. Curcumin main effects on sequential stages of liver pathology

Introduction of liver cancer:-

Primary liver cancer characterised by active neovascularization is among the most common lethal cancers worldwide and can occur at any age. Hepatocellular carcinoma (HCC) occurs in older children and adults and has a high prevalence in developing Asian and African countries. In children under five years of age, hepatoblastoma (HB) accounts for more than 90% of primary hepatic malignant tumors and HCC for 12.5%.[15]

Factors for HCC include cirrhosis, hepatocarcinogenic like aflatoxins and nitrosamines, dietary and environmental carcinogens by generation of reactive oxygen species (ROS) and infections like hepatitis B and C viruses. [56]Chronic liver diseases, viral hepatictis, alcoholism as well as dietary carcinogens, such as aflatoxins and nitrosamines, contribute to HCC.

Liver cancer is diagnosed at an advanced stage quite frequently; hence the available chemotherapy regimens fail to offer a complete cure. Even if chemotherapy has been instituted timely, the available chemotherapeutic agents are reported to show severe adverse effects. Angiogenesis plays a significant role in human HCC tumour progression and recent studies are focussing on anti-angiogenic agents targeting specific tumour vasculature. [16]

The most frequent liver cancer, accounting for approximately 75% of all primary liver cancers, is hepatocellular carcinoma (HCC). HCC is a cancer formed by liver cells, known as hepatocytes that become malignant. In terms of cancer deaths, worldwide HCC is considered the 3rd most common cause of cancer mortalities. [17]

It occurs in the setting of chronic liver inflammation, and is most closely linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins such as alcohol, aflatoxin, or pyrrolizidine alkaloids. Certain diseases, such as hemochromatosis and alpha 1-antitrypsin deficiency, markedly increase the risk of developing HCC. Metabolic syndrome and NASH are also increasingly recognized as risk factors for HCC.[18]

In this regard, discovery of natural phytocompounds having anti-tumor and anti-angiogenic activities could have greater clinical significance as they do not affect physiology and survival of normal cells. Many phytochemicals have proven anti-tumor action including catechins, quercetin in apples and onions, resveratorl in grapes, red wine, peanuts, and ellagic acid in pomegranates. [19,20] .In this current project describes firstly the molecular pathology of liver cancers and then summaries the evidence based literature that describes the various proven mechanism demonstrating the anti-tumor potential of curcumin in turmeric (Curcuma longa) and thus exploring its role as an adjuvant therapeutic remedy for liver cancer.

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

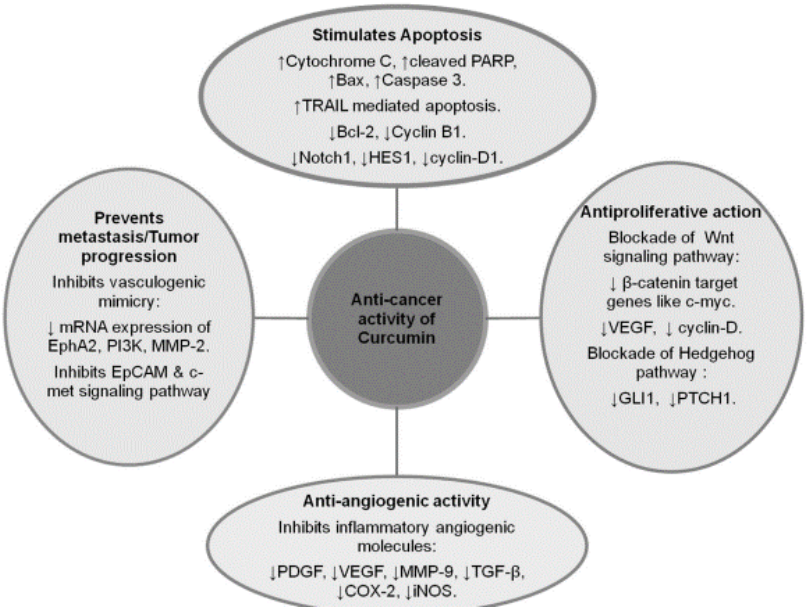
www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

Tumorigenesis and Molecular Biology of Liver Cancer-

Growth factors like hepatocyte growth factor, epidermal growth factor and transforming growth factor (TGF)-alpha control normal hepatic regeneration via DNA synthesis stimulation. TGF-β and activing serve as negative feedback mechanisms and regulate the end point of the hepatocyte proliferation. This termination is regulated by the ratio of liver to body mass thus providing a check on the extent of liver regeneration.[21]

Liver stem cells are proposed to be from dual oriins, intrahepatic with short-term proliferative capacity present within the canals of Herring and interlobular bile ducts and extrahepatic derived from bone marrow and peripheral blood cells with long-term proliferation capacity.[22]



Flow chart depicting the various anti-cancer properties of curcumin. VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinase; PDGF: platelet derived growth factor; TGF: transforming growth factor; COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; EpCAM: epithelial cell adhesion molecule

2. ANTI-TUMOR PROPERTIES OF CURCUMIN

As an anti-tumor agent, curcumin has been reported to exhibit direct action by inhibiting proliferation of tumor cells as well as an indirect action by inhibiting angiogenesis

2.1 Curcumin stimulates apoptosis of cancer cells-

Apoptosis or programmed cell death can be triggered by extrinsic and intrinsic pathways.[23] Intrinsic pathway is stimulated by internal stimuli such as DNA abnormality, hypoxia, viral infection, cellular distress, etc. Extrinsic (receptor mediated) pathway is initiated by extracellular messenger proteins such as TNF. Intrinsic pathway is regulated by the members of the Bcl-2 family of proteins

2.2 Curcumin affects the following pathways and promotes apoptosis of cancer cells-

EF24 is a synthetic compound and a potent curcumin analogue with enhanced bioavailability.[24]Demonstrated that EF24 significantly suppressed HCC and induced apoptosis in mouse liver cancer cell line.

EF24 induces cell cycle arrest at G2/M phase in mouse liver cancer cells. Passage from G2 to M-phase requires the activation of cdc2 by cyclin B1. With the use of curcumin, the levels of cyclin B1 and cdc2 in the cells were significantly reduced. [25]Showed that treatment with curcumin resulted in the activation of Chk1 mediated G2 checkpoint which caused the induction of G2/M arrest and resistance of cancerous cells to curcumin induced apoptosis. In hepatoma cell lines Chk1-mediated activation of G2 checkpoint was required for curcumin induced G2/M arrest. Chk1 inhibition reversed this arrest significantly and sensitizes curcumin resistant cells to apoptosis. Single knockdown of Chk1 in Hep3B cells caused the abrogation of curcumin-induced G2/M arrest and decreased phosphorylation of Cdk1. Thus G2/M arrest is Chk1-mediated and may be responsible for the resistance of cancer cells to curcumin-induced apoptosis. [26]

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) can induce apoptosis in cancer cells by binding to four types of membrane bound death receptors (DR4, DR5, DcR1 and DcR2).Established that curcumin sensitizes human renal cancer cells to TRAIL mediated apoptosis. Membrane bound death receptors DR4 and DR5 have a

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

conserved cytoplasmic region called the death domain which is necessary for TRAIL-induced apoptosis. [27] TRAIL induces apoptosis only in the cancer cells without any toxicity to normal cells because normal cells have decoy receptors on their surface. [28]

When the pathway is unregulated, it behaves as an oncogene and hence it results in increased cell proliferation, prevention of differentiation and inhibition ofapoptosis. [29]Proved that curcumin has inhibitory effects on Notch1 signaling and its target genes (Hes1 and cyclin D1).

3. CYTOTOXIC/ANTI-PROLIFERATION ACTIVITY OF CURCUMIN

Curcumin has been shown to prevent inflammationan increase in HepG2 cells (Hepatoma cell line) in volume and a time-dependent approach to in vitro studies.[30] Curcumin indicates an anti-growth action with two blocks important means; Wnt signature method and Hedgehog Road. Both of these approaches affect cancer stem cells.

3.1 Blockade of the Wntsignaling pathway-Wntsignaling pathways have important role in carcinogenesis as well as embryonic development.Wnt proteins can activate different pathways but canonical wnt/β-catenin pathway is the most studied. Curcumin has been shown to interrupt this pathway and thus suppress the expression of β-catenin target genes like c-myc, VEGF, cyclin-D. Curcumin has been reported to suppress cell proliferation and induced apoptosis by interrupting wntsignaling via decreasing β-catenin activity.[31] Curcumin and its reduced analogue tetrahydrocurcumin showed anti-proliferative effects on HepG2 cell lines.[32] HepG2 cells (hepatoma cell line) when treated with novel curcumin derivative and mesenchymal stem cells showed a significantly decrease of proliferation rate as compared to the control group.[33]Curcumin significantly suppressed the cell proliferation, decreased the β-catenin accumulation and induced apoptosis in human HCC cell lines BEL-7402 and QGY-7703 in a dose dependent manner. A dose dependent decrease in the expressions of c-myc and VEGF was also reported. Thus curcumin attenuated wnt signals in HCC cells. [31]

3.2 Blockade of the Hedgehog pathway-The Hedgehog pathway is another potential target for cancer stem cell eradication. In liver cells, the suppression of the Sonic Hedgehog pathway by small interfering RNA decreased HCC cell proliferation also chemosensitized the cells to 5-fluorouracil and induction of cell apoptosis.[34] In HB, blocking the Hh Hedgehog signaling pathway with an antagonist cyclopamine strongly inhibited cell proliferation of HB cell lines.[56] A significant decrease in expression of Notch1, Hes1 and cyclin D1 was observed in HepG2 cells upon treatment of hepatoma cell lines (HepG2) with mesenchymal stem cells conditioned medium (MSCs CM) and novel curcumin derivative (NCD).[33]

3.3 Induce differentiation of cancer stem cell- Cancer stem cells comprising a small proportion of cancer cells sustain tumor growth and are more resistant to conventional chemotherapy than other more differentiated cancer cells. Malignancy may thus be treated by inducing the differentiation of cancer stem cells and thus making them lose their self-renewal property. Curcumin has been shown to induce differentiation of embryonic stem cells through possible modulation of nitric oxide-cyclic GMP pathway. [35]

4. ANTI-ANTIANGIOGENIC EFFECTS OF CURCUMIN

Active neovascularisation is a predominant feature in HCC and supports tumor growth. Angiogenesis starts when tumor cells start sending signals to the nearby surrounding normal host tissue and encourage the release of signaling molecules that initiate and promote angiogenesis. This angiogenesis provides the tumor cells with oxygen and nutrients and also a route to enter general circulation. HCC cells secrete various angiogenesis activators like VEGF, platelet derived growth factor, TGF-β. Among these, VEGF is most critical antigenic factor.[36] Cancer cells grow in hypoxic conditions that lead to expression of several hypoxia response genes which are involved in metabolic dysregulation.[37] These include inflammatory angiogenic molecules secreted by tumor cells like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase. Angiogenesis requires the expressions of COX-2, VEGF and matrix metalloproteinase-9 (MMP-9). Anti angiogenic effects of curcumin have been demonstrated.[57] COX-2 and VEGF are associated with angiogenesis in HCC.[38] ROS generated as a result of oxidative stress in the cells also causes up regulation of MMPs that causes angiogenesis and invasiveness.[39] Curcumin treatment inhibited the cell proliferation and induce apoptosis in cancer cells. Curcumin also exhibited inhibitory action on cancer metastasis by inhibiting the secretion of MMP-9. [58]

4.1 Metastasis and tumor progression-

a) TNF-α inhibition- TNF-α has a very important role in tumor cell survival and metastasis. Curcumin inhibits TNF-α expression. However, the hydrophobicity and low bioavailability of curcumin are the major barriers. Thus, scientists have encapsulated curcumin in microcells to make it a sustained release preparation in order to increase its solubility

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

and bioavailability.[40] Moreover curcumin bearing microcells significantly reduced the levels of the liver enzymes in HCC induced animal group as compared to the free form curcumin.

b) DNA damage induced by curcumin-Mitochondrial DNA (mDNA), being in closer contact to ROS produced in mitochondria, is more prone to oxidative damage.Mitochondrial and nuclear DNA damage induced by curcumin in human hepatoma (HepG2) cells, a cell line that retains many characteristics of hepatocytes. Furthermore, QPCR assay revealed that curcumin led to dose dependent damage in nuclear as well as mitochondrial genomes. [41]

c)EpCAM as a target in cancer therapy-EpCAM is potentially a promising target as it is highly expressed in most cancer cells as well as on cancer stem cells. In normal tissue, EpCAM is localized to basolateral membranes. Thus, the ease of access for EpCAM-binding antibodies is

lower for normal cells than for cancer cells. EpCAM is strongly over expressed in cancer cells and thus might be partly unbound and more accessible for targeting antibodies and curcumin-loaded lipid-polymer-lecithin hybrid nanoparticles have been used against EpCAM for targeted delivery to colorectal adenocarcinoma cells. [42]

5. ROLE OF CURCUMIN IN DECREASING ADVERSE EFFECTS OF CHEMOTHERAPY

5.1 Neuroprotective effect of curcumin- Cisplatin is potent chemotherapeutic agent with adverse effects like nephrotoxicity and peripheral neuropathy.The neuroprotective effect of curcumin against cisplatin induced cytotoxicity without any interference of curcumin with the cytotoxic activity of cisplatin. [42]

5.2 Anti-inflammatory action- Curcumin has proven anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, immunostimulant, antiseptic, and antimutagenic properties.[43] Thisantiinflammatory action of turmeric helps to decrease the side effects like gastro intestinal inflammation due to chemotherapy or radiotherapy.

5.3 Anti-infective action-Patients who receive chemotherapy are immunocompromised and prone to multiple infections. Curcumin with its beneficial anti-infective action would help to prevent infections and take care of minor infections. [44, 45]

6. SIDE EFFECT OF CURCUMIN

It is important to remember that turmeric used in cooking is very safe. But we don't know how safe curcumin is when used for medical reasons. So far, research studies seem to show that it causes few or no side effects. But we don't know much about the side effects of taking it in large amounts to treat or prevent cancer.

Fortodol contains the strong anti-inflammatory drug nimesulide. Nimesulide can cause severe damage to the liver. The signs include:

- yellowing skin (jaundice)
- dark urine
- feeling or being sick
- unusual tiredness
- stomach or abdominal pain
- loss of appetite

7. ANTI-TUMOR ACTION OF CURCUMIN IN OTHER CANCER

7.1 Colorectal Cancer- Curcumin was studied for both tumor prevention and chemotherapy. In cancer prevention, it was demonstrated to reduce by 40% the formation of aberrant crypt foci in smoking patients (intake of 4 g/day for one month). In a combination study, curcumin, and quercetin (1440 + 60 mg/day for six months) were shown to reduce the number and size of polyps in patients with familial adenomatous polyposis, a hereditary disorder characterized by the development of hundreds of colorectal adenomas which turn malign when left untreated.[46] In chemotherapy, 1 g/day curcumin for up to one month (prior to surgical removal of the tumor) was shown to improve the patient's body weight and to increase the apoptosis rates of the patient's tumor cells.[47]

7.2 Prostate Cancer-A trial has demonstrated that curcumin/flavone association reduces the chances of developing cancer by lowering the levels of prostate-specific antigen (PSA). PSA levels are increased due to the presence of chronic inflammation in the prostate, which is one of the most significant causes of tumorigenesis. Association of curcumin (5.4 g/day for seven days around chemotherapy) with docetaxel/prednisone (75 mg/m + 24 mg, once every three weeks, for six cycles) demonstrated encouraging results, with a tumor objective response in 40% and a PSA response in 59% of the patients in a group having castration-resistant prostate cancer . There is also preliminary evidence on the ability to reduce the formation of metastases. An association of polyphenols (pomegranate seed, green tea, broccoli, and turmeric), taken over six months, has lowered PSA by 63.8% (compared to placebo) in

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor: 5.725

www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 05, May 2024, pp: 2343-2352

prostatectomized patients. Note that, since these men have no prostate, PSA is produced only by neoplastic cells, thus being a good indicator of metastasis growth. Curcumin can confer radioprotective effect in patients with prostate cancer who undergo radiation therapy, reducing the severity of radiotherapy related urinary symptoms. Patients were given 3 g of curcuminoids per day (corresponding to ca. 2 g/day of curcumin) for one week before the onset of radiotherapy and until completion of radiotherapy.[48,49]

7.3 Breast Cancer- Curcumin was used in co-therapy with both chemotherapeutic agents and radiation. A combination therapy with docetaxel and curcumin (in escalating doses of up to 6 g/day) was found to afford better therapeutic results than docetaxel used alone: histological improvements were observed in the fourteen patients under study, all having reduction or elimination of disseminated foci . Curcumin was evaluated in two clinical trials regarding protective action against radiation-induced dermatitis during radiotherapy of breast cancer patients. Despite promising results on a pilot study, with slightly less severe dermatitis in the curcumin group, a second trial on 686 patients showed no significant changes in pain, symptoms, and quality of life of the patients taking curcumin (1.5 g daily) in regard to those taking placebo.[50]

7.4 Pancreatic cancer-: A phase II study with twenty-one patients taking curcumin (8 g/day for up to 18 months) showed partial regression during the treatment period; patients had different responses after treatment, one of them having become stable and another one having shown a strong tumor relapse. Another trial evaluated the association of curcuminoids (8 g/day, corresponding to 6.14 g/day of curcumin) with a gemcitabine-based chemotherapeutic treatment. A total of 21 patients was divided into two groups: one, with 2 patients, received gemcitabine monotherapy; the other, with 19 patients, received a combination therapy of gemcitabine and S-1. S-1 is a novel oral antitumor formula based on fluorouracil, comprising three pharmacological agents: (i) tegafur, a prodrug of 5- fluorouracil, (ii) 5-chloro-2, 4-dihydroxypyridine, which inhibits dihydropyrimidine dehydrogenase activity; and (iii) potassium oxonate, which reduces gastrointestinal toxicity was also evaluated. Eighty-one percent of the patients died during the study period. In the surviving patients, the treatment was able to stabilize the disease.[51]

8. DIOGNOSIS OF LIVER CANCER

8.1 Physical examination- If a person has symptoms of HCC, the doctor will feel the abdomen to check for lumps, swelling, or other changes in the liver, spleen, and other nearby organs. The doctor will also look for an abnormal buildup of fluid in the abdomen and for signs of jaundice, including yellowing of the skin and whites of the eyes.

8.2 Blood tests-At the same time as the physical examination, the doctor will most likely do a blood test to look for a substance called AFP. In the United States, AFP is found in elevated levels in the blood of about 50% to 70% of people who have HCC. The doctor will also test the person's blood to see if there is hepatitis B or C. Other blood tests can show how well the liver is working.

8.3 Ultrasound-An ultrasound uses sound waves to create a picture of the structures inside the body, using a small amount of radiation. The sound waves bounce off the liver, other organs, and tumors. Each creates a different picture on a computer monitor.

8.4 Computed tomography (CT or CAT) scan-A CT scan creates a 3-dimensional image of the inside of the body using x-rays taken from different angles. A computer combines these pictures into a detailed, cross-sectional view that shows any abnormalities or tumors. Sometimes, a special dye called a contrast medium is given before the scan to provide better detail on the image. This dye can be injected into a patient's vein or given as a liquid to swallow. Often, HCC can be diagnosed based on features specific to the cancer that are seen on a CT scan. This helps patients avoid a liver biopsy (see below). A CT scan can be used to measure the tumor's size.

8.5 Magnetic resonance imaging (MRI) -An MRI uses magnetic fields, not x-rays, to produce detailed images of the body. MRI can be used to measure the tumor's size. A special dye called a contrast medium is given before the scan to create a clearer picture. This dye can be injected into a patient's vein or given as a liquid to swallow.

8.6 Laparoscopy-Laparoscoy is a test that allows the doctor to see inside the body with a thin, lighted, flexible tube called a laparoscope. The person is sedated as the tube is inserted through a small incision in the abdomen. Sedation uses medication to make the person relaxed and sleepy. Local anesthetic is also used to numb the area. Laparoscopy is used very rarely in diagnosing liver cancer.

8.7 Biopsy- A Biopsy is the removal of a small amount of tissue for examination under a microscope. A pathologist then analyzes the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease. The type of biopsy performed will depend on the location of the cancer. The biopsy can be done during a laparoscopy, a fine-needle aspiration, or a core biopsy. During a fine-needle aspiration, cells are removed using a thin needle inserted into the tumor. A core biopsy uses a thicker needle. Either

procedure is done by a radiologist who uses an ultrasound to direct the needle to the particular part of the liver with the tumor. The actual biopsy procedure usually lasts for less than 1 minute. It is typically not painful, and few people have complications from the procedure.

9. CONCLUSION

Liver cancer is a leading cause of death in children and adults. The treatment revolves around chemotherapy, radiotherapy and surgery. Recent advances include transcatheter arterial chemoembolization, radioembolization, anti-angioigenic drugs like sorafenib and liver transplantation in advanced stages.The conventional anticancer therapies reduce the tumor mass, but potentially leave behind cancer-initiating cells. Thus, new combinations of therapies may be needed to overcome the complex network of signaling pathways, and ultimately inhibit the signaling that controls tumor growth and survival. Adjuvant curcumin along with the current modalities of treatment may help to overcome the side effects and also have synergistic action as an anti-cancer agent.

Curcumin has been reported to inhibit telomerase activity in human cancer cell lines.[52] Synergistic anti-cancer effects of curcumin has also been demonstrated in conjunction with chemotherapeutic drugs such as doxorubicin and paclitaxel by in vivo animal models, and with cisplatin, 5-FU, and adriamycin by in vitro studies.[53,54]

Thus, to conclude, curcumin has a lot of potential to act as an adjuvant remedy in liver cancer. As far as toxicity issue is concerned, herbal medicines are much safer, have less adverse effects and relatively cheaper than conventional medicines. Curcumin as an adjunct would have a synergistic anti-cancer action and would also protect against the side effects of the current chemotherapeutic agents. Previous studies have also claimed its antitumor e53ffects against various types of cancers due to its inhibitory effects on many types of pathways. In this article we have discussed various pharmacological activities of curcumin along with its various antitumor mechanisms.

Curcumin has the ability to modify many signaling pathways demonstrating its anti-tumor potential. Also, we noticed that curcumin has been proved to possess strong anti-oxidant andanti-inflammatory properties. Curcumin also targets principal anti-antigenic molecules like VEGF and COX-2. All these properties of curcumin are essential for its use as a therapeutic anti-tumor agent. It provides a future perspective for the development of a novel adjuvant anticancer agent for humans. Poor bioavailability and hydrophobicity of curcumin are the main obstacles in its path to be used clinically as an anti-tumor agent. However this issue can be resolved with the advancements in the drug delivery like formation of nanoparticles and microcells of curcumin via polymerization and these can be used to target cancerous cells without affecting other normal cells. Thus we can conclude that curcumin might be a promising candidate as an adjuvant therapy for liver cancer in the future but further research is needed to elucidate its various mechanisms of action, to reveal its therapeutic strategy and to titrate the dose required to reap maximum benefit.

10. REFERENCES

[1] Akram, M.; Uddin, S.; Ahmed, A.; Khan, U.; Hannan, A.; Mohihuddin, E.; Asif, M. Curcuma Longa and Curcumin. Rom. J. Biol. Plant. Biol. 2010, 55, 65–70.

[2] Prasad, S.; Aggarwal, B.B. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In Herbal Medicine: Biomolecular and Clinical Aspects, 2nd ed.; Benzie, I.F.F., Wachtel-Galor, S., Eds.; CRC Press: Boca Raton, FL, USA, 2011.

[3] Govindarajan, V.; Stahl, W.H. Turmeric—chemistry, technology, and quality. CRC Crit. Rev. Food Sci. Nutr. 1980, 12, 199–301.

[4] Priyadarsini, K.I. The Chemistry of Curcumin: From Extraction to Therapeutic Agent. Molecules 2014, 19, 20091–20112.

[5] Carvalho, D.D.M.; Takeuchi, K.P.; Geraldine, R.M.; De Moura, C.J.; Torres, M.C.L. Production, solubility and antioxidant activity of curcumin nanosuspension. Food Sci. Technol. 2015, 35, 115–119.

[6] Hatcher, H.; Planalp, R.; Cho, J.; Tortia, F.M.; Tortic, S.V. Curcumin: From ancient medicine to current clinical trials. Cell. Mol. Life Sci. 2008, 65, 1631–1652.

[7] Priyadarsini, K.I. Photophysics, photochemistry and photobiology of curcumin: Studies from organic solutions, bio-mimetics and living cells. J. Photochem. Photobiol. C Photochem. Rev. 2009, 10, 81–95.

[8] Khurana, A.; Ho, C.-T. High Performance Liquid Chromatographic Analysis of Curcuminoids and Their Photo-oxidative Decomposition Compounds in Curcuma Longa L. J. Liq. Chromatogr. 1988, 11, 2295–2304.

[9] Tønnesen, H.H.; Karlsen, J.; van Henegouwen, G.B. Studies on Curcumin and Curcuminoids VIII. Photochemical Stability of Curcumin. Z. Lebensm. Unters. Forsch. 1986, 183, 116–122.

[10] Kim, Y.-J.; Lee, H.J.; Shin, Y. Optimization and validation of high-performance liquid chromatography method for individual curcuminoids in turmeric by heat-refluxed extraction. J. Agric. Food Chem. 2013, 61, 10911–10918.

[11] Kurmudle, N.; Kagliwal, L.D.; Bankar, S.B.; Singhal, R.S. Enzyme-assisted extraction for enhanced yields of turmeric oleoresin and its constituents. Food Biosci. 2013, 3, 36–51.

[12] Ali, I.; Haque, A.; Saleem, K. Separation and identification of curcuminoids in turmeric powder by HPLC using phenyl column. Anal. Methods 2014, 6, 2526–2536.

[13] Sun, X.; Gao, C.; Cao, W.; Yang, X.; Wang, E. Capillary elelctrophoresis with amperometric detection of curcumin in Chinese herbal medicine pretreated by solid-phase extraction. J. Chromatogr. A 2002, 962, 117–125.

[14] Sun, X.; Gao, C.; Cao, W.; Yang, X.; Wang, E. Capillary elelctrophoresis with amperometric detection of curcumin in Chinese herbal medicine pretreated by solid-phase extraction. J. Chromatogr. A 2002, 962, 117–125.

[15] Litten JB, Tomlinson GE. Liver tumors in children. Oncologist 2008;13:812-20.

[16] Chintana P. Role of curcumin on tumor angiogenesis in hepatocellular carcinoma. NaresuanUniv J 2008;16:239-54.

[17] *Mokdad, Ali A.; Singal, Amit G.; Yopp, Adam C. (2015-12-22). "Liver Cancer"*. JAMA. 314 (24): 2701.

[18] Kumar V, Fausto N, Abbas A, eds. (2015). *Robbins &Cotran Pathologic Basis of Disease* (9th ed.). Saunders. pp. 870–873.

[19] Lee EO, Lee HJ, Hwang HS, Ahn KS, Chae C, Kang KS, Lu J, Kim SH. Potent inhibition of Lewis lung cancer growth by heyneanol A from the roots from the Vitisamurensis through apoptotic and antiantigenic activities. Carcinogenesis 2006;27:2059-69.

[20] Mann CD, Neal CP, Garcea G, Manson MM, Dennison AR, Berry DP. Phytochemicals as potential chemopreventive and chemotherapeutic agents in hepatocarcinogenesis. Eur J Cancer Prev2009;18:13-25.

[21] Michalopoulos GK. Liver regeneration. J Cell Physiol2007;213:286- 300.

[22] Alison MR. Liver stem cells: implications for hepatocarcinogenesis. Stem Cell Rev 2005;1:253-60.

[23] He, Z.; Shi, C.-B.; Wen, H.; Li, F.-L.; Wang, B.-L.; Wang, J. Upregulation of p53 Expression in Patients with Colorectal Cancer by Administration of Curcumin. Cancer Investig. 2011, 29, 208–213.

[24] Ziegler DS, Kung AL. Therapeutic targeting of apoptosis pathways in cancer. CurrOpinOncol2008;20:97-103.

[25] Liu H, Liang Y, Wang L, Tian L, Song R, Han T , Pan S, Liu L. In vivo and in vitro suppression of hepatocellular carcinoma by EF24, a curcumin analog. PLoS One 2012;7:e48075.

[26] Wang WZ, Cheng J, Luo J, Zhuang SM. Abrogation of G2/M arrest sensitizes curcumin-resistant hepatoma cells to apoptosis. FEBS Lett 2008;582:2689-95.

[27] Jung EM, Lim JH, Lee TJ, Park JW, Choi KS, Kwon TK. Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen speciesmediated upregulation of death receptor 5 (DR5). Carcinogenesis 2005;26:1905-13.

[28] Ashkenzi A, Dixit VM. Apoptosis control by death and decoy receptors. CurrOpin Cell Biol1999;11:255-60.

[29] Yin L, Velazquez OC, Liu ZJ. Notch signaling emerging molecular 70 Hepatoma Research | Volume 2 | March 9, 2016 targets for cancer therapy. BiochemPharmacol2010;80:690-70.

[30] Dai X, Yin H, Sun L, Hu X, Zhou C, Zhou Y Zhang W, Huang XE, Li XC. Potential therapeutic efficacy of curcumin in liver cancer. Asian Pac J Cancer Prev2013;14:3855-9.

[31] Xu MX, Zhao L, Deng C, Yang L, Wang Y, Guo T, Li L, Lin J, Zhang L. Curcumin suppresses proliferation and induces apoptosis of human hepatocellular carcinoma cells via the wntsignaling pathway. Int J Oncol2013;43:1951-9.

[32] Yoysungnoen P, Wirachwong P, Changtam C, Suksamrarn A, Patumraj S. Anti-cancer and anti-antigenic effects of curcumin and tetrahydrocurcumin on implanted hepatocellular carcinoma in nude mice. World J Gastroenterol2008;14:2003-9.

[33] Aziz MTA, Khaled HM, Hindawi AE, Roshdy NK, Rashed LA, SabryD ,Hassouna AA, Taha F, Ali WI. Effect of mesenchymal stem cells and novel curcumin derivative on Notch1 signaling in hepatoma cell line. Biomed Res Int 2013;2013:e129629.

[34] Aza-Blanc P, Kornberg TB. Ci: a complex transducer of the hedgehog signal. Trends Genet 1999;15:458-62.

[35] Sicklick JK, Li YX, Jayaraman A, Kannangai R, Qi Y, Vivekanandan P, Ludlow JW, Owzar K, Chen W, Torbenson MS, Diehl AM. Dysregulation of the Hedgehog pathway in human hepatocarcinogenesis. Carcinogenesis 2006;27:748-57.

[36] Chintana P. Role of curcumin on tumor angiogenesis in hepatocellular carcinoma. NaresuanUniv J 2008;16:239-54.

[37] Fox SB, Gasparini G, Harris AL. Angiogenesis: Pathological, prognostic and growth factor pathways and their link to trial design and anticancer drugs. Lancet Oncol2001;2:278-89.

[38] Cheng AS, Chan HL, To KF, Leung WK, Chan KK, Liew CT, Sung JJ. Cyclooxigenase-2 pathway correlates with vascular endothelial growth factor expression and tumor angiogenesis in hepatitis-B virus-associated hepatocellular carcinoma. Int J Oncol2004;24:853.

[39] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation and cancer: how are they linked? Free RadicBiol Med 2010;49:1603-16.

[40] Farazuddin M, Dua B, Zia Q, Khan AA, Joshi B, Owais M. Chemotherapeutic potential of curcumin bearing microcells against hepatocellular carcinoma in model animals. Int J Nanomedicine2014;9:1139-52.

[41] Cao J, Jia L, Zhou HM, Liu Y, Zhong LF. Mitochondrial and nuclear DNA damage induced by curcumin in human hepatoma G2 cells. ToxicolSci2006;91:476-83.

[42] Li L, Xiang D, Shigdar S, Yang W, Li Q, Lin J, Liu K, Duan W. Epithelial cell adhesion molecule aptamer functionalized PLGAlecithin-curcumin-PEG nanoparticles for targeted drug delivery to human colorectal adenocarcinoma cells. Int J Nanomed2014;9:1083- 96.

[43] Julie SJ. Anti-inflammatory properties of curcumin, a major constituent of curcuma longa: a review of preclinical and clinical research. Altern Med Rev 2009;1:141-53.

[44] Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol2009;41:40-59.

[45] Sandur SK, Ichikawa H, Pandey MK, Kunnumakkara AB, Sung B, Sethi G, Aggarwal BB. Role of prooxidants and antioxidants in the anti-inflammatory and apoptotic effects of curcumin (diferuloylmethane). Free RadicBiol Med 2007;43:568-80.

[46] Cruz–Correa, M.; Shoskes, D.A.; Sanchez, P.; Zhao, R.; Hylind, L.M.; Wexner, S.D.; Giardiello, F.M. Combination Treatment With Curcumin and Quercetin of Adenomas in Familial Adenomatous Polyposis. Clin. Gastroenterol. Hepatol. 2006, 4, 1035–1038, doi:10.1016/j.cgh.2006.03.020.

[47] He, Z.; Shi, C.-B.; Wen, H.; Li, F.-L.; Wang, B.-L.; Wang, J. Upregulation of p53 Expression in Patients with Colorectal Cancer by Administration of Curcumin. Cancer Investig. 2011, 29, 208–213.

[48] Taleban, R.R.F.-A.; Hejazi, J. A Pilot Clinical Trial of Radioprotective Effects of Curcumin Supplementation in Patients with Prostate Cancer. J. Cancer Sci. Ther. 2013, 5, 320–324.

[49] Hejazi, J.; Rastmanesh, R.; Taleban, F.-A.; Molana, S.-H.; Hejazi, E.; Ehtejab, G.; Hara, N. Effect of Curcumin Supplementation During Radiotherapy on Oxidative Status of Patients with Prostate Cancer: A Double Blinded, Randomized, Placebo-Controlled Study. Nutr. Cancer 2016, 68.

[50] Ryan, J.L.; Heckler, C.E.; Guido, J.J.; Peoples, A.R.; Gewandter, J.S.; Ling, M.; Vinciguerra, V.P.; Anderson, T.; Evans, L.; Wade, J.; et al. Oral curcumin for radiation dermatitis: A URCC NCORP study of 686 breast cancer patients. Support. Care Cancer 2017, 26, 1543–155.

[51] Kanai, M.; Yoshimura, K.; Asada, M.; Imaizumi, A.; Suzuki, C.; Matsumoto, S.; Nishimura, T.; Mori, Y.; Masui, T.; Kawaguchi, Y.; et al. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. Cancer Chemother. Pharmacol. 2010, 68, 157–164.

[52] Cui S, Qu X, Xie Y, Zhou L, Nakata M, Makuuchi M, Tang W. Curcumin inhibits telomerase activity in human cancer cell lines. Int J Mol Med 2006;18:227-31.

[53] Zhao X, Chen Q, Liu W, Li Y, Tang H, Liu X, Yang X. Codelivery of doxorubicin and curcumin with lipid nanoparticles results in improved efficacy of chemotherapy in liver cancer. Int J Nanomedicine2014;10:257-70.

[54] Ganta S, Devalapally H, Amiji M. Curcumin enhances oral bioavailability and anti-tumor therapeutic efficacy of paclitaxel upon administration in nanoemulsion formulation. J Pharm Sci2010;99:4630-41.

[55] Esatbeyoglu, T.; Huebbe, P.; Insa, M.A.; DawnChin, E.; Wagner, A.E.; Rimbach, G. Curcumin—From Molecule to Biological Function. Angew. Chem. Int. Ed. 2012, 51, 5308–5332.

[56] Darvesh AS, Aggarwal BB, Bishayee A. Curcumin and liver cancer: a review. Curr Pharm Biotechnol2012;13:218-28.

[57] Liu XM, Zhang QP, Mu YG, Zhang XH, Sai K, Pang JCS, Ng HK, Chen ZP. Clinical significance of vasculogenic mimicry in human gliomas. J Neurooncol2011;105:173-9.

[58] Mandal, V.; Mohan, Y.; Hemalatha, S. Microwave assisted extraction of curcumin by sample-solvent dual heating mechanism using Taguchi L9 orthogonal design. J. Pharm. Biomed. Anal. 2008, 46, 322–327.