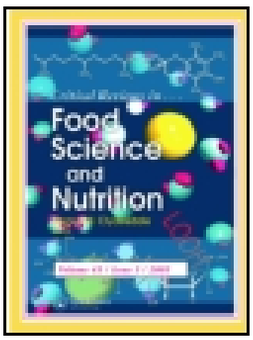

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Cucurmin, anticancer, & antitumor perspectives: A comprehensive review

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ABSTRACT

Cucurmin, a naturally yellow component isolated from turmeric, ability to prevent various life-style related disorders. The current review article mainly emphasizes on different anticancer perspectives of cucurmin, i.e., colon, cervical, uterine, ovarian, prostate head and neck, breast, pulmonary, stomach and gastric, pancreatic, bladder oral, oesophageal, and bone cancer. It holds a mixture of strong bioactive molecule known as cucurminoids that has ability to reduce cancer/tumor at initial, promotion and progression stages of tumor development. In particular, these compounds block several enzymes required for the growth of tumors and may therefore involve in tumor treatments. Moreover, it modulates an array of cellular progressions, i.e., nitric oxide synthetase activity, protein kinase C activity, epidermal growth factor (EGF) receptor intrinsic kinase activity, nuclear factor kappa (NF-kB) activity, inhibiting lipid peroxidation and production of reactive oxygen species. However, current manuscript summarizes most of the recent investigations of cucurmin but still further research should be conducted to explore the role of curcumin to mitigate various cancers.

KEYWORDS

Turmeric; cucurmin; functional food; bioactive molecules; nutraceuticals and cancer and tumor treatment

Introduction

Spices and herbs possess numerous therapeutics properties by imparting flavor, color, and taste to food preparation and food system. Prehistorically, people utilized plants to cure ailments and relieve physical pain. There is an accepted fact that the traditional medicines has reduced side effects and increased efficiency on human body. Around the world, more than 35,000 plant species are being consumed for medicinal purposes in various nations. Almost, 80% of the world populations for their primary health care depend upon traditional medicines, most of which captivate the plant extracts consumption (Sandhya et al., 2005).

Curcuma longa (turmeric) is a curry spice and a traditional Chinese curative herb, used to consume to overcome inflammatory conditions in Southeast Asia and China (Lestari and Indrayanto, 2014). The rhizome of turmeric has also been utilized by the textile industry as a pigment for dye, as a spice in traditional cuisine. The estimated dietary intake of turmeric is to be approximately 2.5 g/day or 100 mg cucurmin/day (Aggarwal et al., 2004).

Turmeric is used to cure various other common maladies including skin and eye infections, acnes, sprains, wounds, arthritis, dysentery, ulcers, flatulence, and stomach upset (Singh and Singh, 2009, 2010). Turmeric comprises of carbohydrates (69.4%), moisture (13.1%), minerals (3.5%), fat (5.1%), and protein (6.3%). Turmeric includes three curcuminoids (bisdemethoxycurcumin, curcumin, and demethoxycurcumin), volatile oils (tumerone, natlantone, and zingiberone), sugars, proteins, and resins. The concentration of the three major curcuminoids of different samples of *Curcuma longa* presented an average composition of 5.69; among which, 2.86% curcumin, 1.47% desmethoxycurcumin, and 1.36% bidesmethoxycurcumin (Li et al., 2011a). Although, cucurmin chemically comprises of diferuloylmethane (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5 dione), cucurmin also composed of 3–7% bisdemethoxy cucurmin (BDMC), and demethoxy cucurmin (DMC), respectively. However, cucurmin looks more active than BDMC or DMC (Gupta et al., 2012; Sandur et al., 2007).

The food and pharmacy domains have extensively researched curcumin with models in vitro to analyze the curcuminoids antioxidant activity. The studies presented that the desmethoxycurcumin and the bisdesmethoxycurcumin along with curcumin are also satisfactory antioxidants. Comprehensive reviews characterized that curcumin is an exceptional molecule among many other naturally occurring compounds for cancer therapeutics. Pleiotropic properties of curcumin molecule facilitate it to target the genome (DNA), messenger (RNA), and enzymes (proteins) within cells, actions that can be sequential. Unlike other chemotherapeutic agents, curcumin exhibits pleiotropic properties that involve the variation of nuclear factor—kappa B (NF-kappa B), transcript factor activator protein-1 (AP-1), tumor protein 53 (p53), mitogen activated protein kinase (MAPK), and nuclear beta-catenin signaling (Aggarwal et al., 2003; Yallapu et al., 2014).

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Cucurmin has lipophilic nature so it transfuses into cell membrane quickly (Jaruga et al., 1998a). It was observed that cucurmin affects the cell membrane structure as well as its functional role and impersonate distinctive instances ensues during apoptosis; although it was eminent that with typical apoptotic cell death the cellular response to cucurmin results in a loss of membrane integrity was instant, alterable and cells could recuperate in a relatively short time (Jaruga et al., 1998b). It was advised by others that cucurmin induced membranous changes might underlie some of its effects.

Metabolism of cucurmin

Cucurmin is a derivative of hydroxycinnamic acid containing two rings of hydrophobic polyphenolic linked by two carbonyl groups. In intestine, cucurmin metabolism involves the glucuronidation, sulfation, and reduction reactions casing poor systematic absorption (Baum et al., 2008; Ireson et al., 2002). These metabolites have poor cell permeability and very short half-life (Gonzales and Orlando, 2008). In the gastrointestinal tract, cucurmin remains undigested about 40–80% of the total amount ingested, though further metabolism was carried in the intestinal mucosa and liver. Cheng et al. (2001) reported that 10 g/day of cucurmin can be consumed to avoid toxicity in humans. An increase in the absorption is found when cucurmin supplemented with 20 mg of piperine (an alkaloid in black pepper), although it produces side effects (Shoba et al., 1998).

Furthermore, in vitro, a nanoparticle-based form of cucurmin known as "Nano-Cucurmin" has been progressed. It has ability to regulate the bioavailability and solubility of cucurmin. It has also been capable of deteriorating inflammatory response and encouraging the cell death in human pancreatic cancer cell lines (Bisht et al., 2007). It has been investigated in male Wistar rats that cucurmin formulated with phosphatidylcholine can increase the plasma level of cucurmin up to fivefold (Marczylo et al., 2006). Baum et al. (2008) observed that cucurmin provided with stearic acid, olive oil and phosphatidyl choline increase blood cucurmin level. The bioavailability of cucurmin also increased when turmeric spice was added along with oil in food matrix (Lim et al., 2000). The cucurmin serum levels were found to be 50 times higher resulted as a combination of cucurmin and lipids carried in vivo experiment accomplished with murine models.

By far, an upper level of toxicity for cucurmin has not been established, but the research showed that a safe and tolerable dose of cucurmin as high as 12 g/day for humans however, few mild side effects have been reported (Goel et al., 2008; Hsu and Cheng; Manjunatha and Srinivasan, 2006). Moreover, the bulky nature of this compound creates difficulty in executing diet plan if the dose is planned above 8 g (Cheng et al., 2001). The bioavailability of oral cucurmin is minimal whereas the delivery of drug is a major issue because of permutation, rapid elimination, poor gastrointestinal absorption, and poor aqueous solubility (Sharma et al., 2007).

Tetrahydro-cucurmin is the most important and thoroughly studied reduction metabolite among other potentially active metabolites that have been discovered. It does not occur in natural cucurmin sources as it lacks the yellow color and hydrophobicity of cucurmin. When ingesting cucurmin orally, it alters the serum concentration at 1–2 hour and is untraceable by 12 hour. While few researchers claim that serum cucurmin is untraceable below oral doses of about 4 grams (Cheng et al., 2001); whereas, others have identified cucurmin at much lower doses in both serum and urine.

Cucurmin promptly metabolized and conjugated in the liver and excreted in the feces. Due to this phenomenon, the systematic bioavailability of cucurmin is restricted. Particularly, when rats were administered with 40 mg/kg intravenous dose of cucurmin, the complete plasma clearance of this compound endures at the end of 1 hour postdosing. The peak plasma concentration (1.8 ng/mL) was observed when an oral dose of 500 mg/kg were given to rats. Cucurmin glucuronide and cucurmin sulfate were the major metabolites that were being identified (Ireson et al., 2001). The bioavailability and efficient delivery of cucurmin can be made possible by designing and developing its nano formulations (nanoparticles, nanogels, liposomes, etc.) (Mohan Yallapu et al., 2012).

Anticancer perspectives

Colon cancer

Colon cancer is the third main cause of cancerous death and the incidence is rapidly increasing in developing countries. Chemotherapy has significant role to curtail the populace from the colon carcinoma. Multidrug resistance (MDR) has been proved successful treatment for colon cancer due to many cytotoxic agents. MDR is the active export of the drug from cells by the overexpression of P-glycoprotein (P-gp) and other ATP binding cassette (ABC) transporters. Resistance to chemotherapy has been related with the inhibition of apoptosis (Parkin et al., 2005; Song et al., 2012).

Glucose-regulated protein 78 (GRP78) is the basic regulator of endoplasmic reticular (ER) function. Curcumin enhances the sensitivity of overexpressed GRP78 in HT-29 cells. Curcumin enhances the apoptosis level in knotted control cells compared to GRP78KD DLD-1 cells during cell cycle examination and TUNEL assay. It also increased the Bcl-2 level in GRP78KD cells (Shakibaei et al., 2014; Webster et al., 2014). Moreover, it also prevents from the human colon cancer through inhibiting cell proliferation and cell survival, improving cellular uptake, exhibiting controlled release at physiological pH, activating the cascade of caspases and promoting intrinsic apoptotic signaling (Waghela et al., 2015).

TGF-β signaling pathway is a tumor inhibitors, but alterations in TGF-β signaling pathway promotes colon cancer cell growth, migration, invasion, angiogenesis, and metastasis. Curcumin has cytotoxic effect on colon cancer cell lines via inhibiting the TGF-β signaling cascade (Ramamoorthi and Sivalingam, 2014). Curcumin also regulates the cell-cycle regulatory genes and exerts a chemo-preventive effect on colorectal cancer cell lines in mouse xenograft model through up regulating tumor-suppressive miR-34a, down regulating omiR-27a, and regulating specific miRNAs (Toden et al., 2015). Recently, Wang et al. (2015) describe the mechanism prevent from the human colorectal cancer HCT116 and HT29 cells through multiple mechanisms (1) glycolytic inhibition, (2) apoptotic induction (3) down regulation of the expression and activity of

hexokinase II (HKII), (4) mitochondrial-mediated apoptosis, and (5) regulation of HKII in a concentration-dependent manner. Similarly, Guo et al. (2015) investigated the chemotherapeutic role of curcumin against LoVo human colorectal cancer cells via inducing apoptosis, cell cycle capture in S and G2/M phases, reduced expressions of Bax, caspase-3, and poly (ADP-ribose) polymerase (PARP), apoptotic tumor cells and the suppressed the expression of pro-caspase-3, Bcl-2, HSP70, survivin, and pro-PARP, respectively. Furthermore, it also suppressed the metastasis by lowering Zeb 1, Hef 1, and Claudin 1 mRNA levels and can reduced the SW480 cell propagation with IC50values of 15.9, 11.6, and 7.64 μM at 24, 48, and 72 hours posttreatment (Esmatabadi et al., 2015). After 5 days treatment on HT29 cells, curcumin lowered the CpG methylation of the DLEC1 promoter, increased mRNA expression of DLEC1, reduced subtypes of histone deacetylases (HDAC 4, 5, 6, and 8) and protein expression of DNA methyltransferases (Guo et al., 2015). It enhances the expression of pro-apoptotic Bcl-2 family members (Bad and Bax) while lower the anti-apoptotic Bcl-2 protein. It suppresses the Bcl-2 protein due to the presence of several hydrogen bonds at active site and evident by negative glide score of Bcl-2. It has been found anti-neoplastic activity through inducing apoptosis, downregulating PI3-K/Akt/PTEN pathway, decreasing $\Delta\Psi$ M, and increasing ROS generation (Rana et al., 2015). It also prevents from the colorectal carcinogenesis in HT 29 cell line induced by activating PPARy signal transduction pathway (Liu et al., 2015; Toden et al., 2015).

It has chemo-preventive mechanisms against liver metastasis via controlling matrix metalloproteinase-9 (MMP-9) and E-cadherin expression, inhibiting HCT-116 cell migration and invasion (Shen et al., 2014). In colorectal cancer LOVO cells, it enhances the efficacy of irinotecan by inducing apoptosis, suppressing GSTM5 expression to enhance the lethal effect of irinotecan, and inducing apoptosis (Zhu et al., 2013). Moreover, Radhakrishnan et al. (2014) investigated the cytotoxic role of curcumin against HCT116 cells and SW480 cells via lowering the pTyr(421)- Cortactin (CTTN). Curcumin is an activator of non-receptor type 1 protein tyrosine phosphatase (PTPN1) and causes to dephosphorylation of pTyr(421)-CTTN by enhancing its activity. It also suppresses the PTPN1 and decreases the migration of HCT116 and SW480 cells. In colon cancer cell lines, curcumin has an role of activator of PTPN1 by reducing cell motility via dephosphorylation of pTyr(421)-CTTN.

It has been reported that a nanoparticulate formulation of cucurmin encapsulated in stearic acid-g-chitosan oligosaccharide (CSO-SA) polymeric micelles can increase antitumor efficacy and eliminate colorectal cancer stem cells (Wang et al., 2015). In addition to nanoformulations, colon, and testicular cancer can also be controlled effectively through synergistic effect of cucurmin with some other compounds like catechin and bleomycin.

Cervical cancer

In developing countries the cervical cancer is most predominant in women than in men (Singh and Singh, 2010). The infection of papillomaviruses (HPVs) in human causes the progression of cervical cancer, principally by the action of viral oncogenes. The morbidity and mortality rate is reduced due to and the occurrence of cervical cancer by treatment with HPV-related technology. The in vitro cucurmin exhibited antitumor activity in the HPV linked cells (Roy et al., 2002; Sreekanth et al., 2011) and it down-regulate the viral oncogenes, AP-1 and NF-jB (Divya and Pillai, 2006; Limtrakul et al., 2006). In vitro cucurmin controls the function and expression of P-gp in human KB-V1 cells that are multidrug-resistant (Aggarwal et al., 2007; Chearwae et al., 2004) and it also induces the cisplatin-induced apoptosis by sensitizing the SiHa cells which are cisplatin-resistant. This directs the cucurmin's potential to reverse the MDR in cervical cancer cells. Goel et al. (2008) suggested that cucurmin taken orally in a daily dose of 0.5–12 g for 3 months leads to histologic improvement in uterine and cervical intraepithelial carcinoma's precancerous lesions. This improvement in lesions was seen in one out of four patients that have uterine and cervical carcinomas (Singh and Singh, 2009).

In anti-carcinogenic role, curcumin down regulates TGF-β signaling pathway by lowering the expression of Smad4, P-Smad3, and TGF-β Receptor II. It also has anti-tumorigenic effects on TGF-β through suppressing the TGF-β induced migration and invasion. It also suppresses the downstream effectors of TGF-β signaling pathway, p21, cyclinD1, and Pin1, and also down regulates the mesenchymal markers (Snail and Slug) in cervical cancer cell lines. Moreover, curcumin also prevent from the SiHa and HeLa cells via down regulating the Wnt/β-catenin signaling pathway by suppressing β-catenin (Thacker and Karunagaran, 2015). Likewise, curcumin has antiproliferative role against different cervical cancer cells lines, i.e., C33A, CaSki, HeLa, and ME180. They induce apoptosis, activating ER resident UPR sensors including IRE-1α, PERK, and ATF6, and their downstream signaling proteins as well as also activates the CHOP. Curcumin also reduces anti-apoptotic protein Bcl-2 to pro-apoptotic protein Bax expression ratio promotes the ER stress-mediated apoptosis and also enhances the cell type-specific ROS generation (Kim et al., 2015). Yoysungnoen et al. (2015) investigated the preventive role of tetrahydrocurcumin (100, 300, and 500 mg/kg) daily for 30 consecutive days against cervical cancer- (CaSki-) of female BALB/c nude mice. It significantly lowered VEGF, VEGFR-2, and HIF-1α expressions.

A large number of clinical studies have been proved the anticancer effect against cervical cancer cell lines. Yoysungnoen et al. (2015) determined the role of curcumin (1,000 and 1,500 mg/kg) suppressed the tumor growth and angiogenesis in CaSki-implanted mice via downregulating VEGF, COX-2 and EGFR (Lewinska et al., 2014). In 2 human cervical cancer cell lines, curcumin exerts anticancer activity in CaSki [human papilloma virus (HPV)16-positive] and HeLa (HPV18-positive) cell lines through inducing apoptosis, increasing the expression levels of p53 protein and cleaved caspase-3. Moreover, curcumin lowers the levels of phosphorylation of IκBα and the p65-NF-κB subunit in CaSki cells whilst induce apoptosis in HPV-positive human cervical cancer cell lines via the NF-κB-p53-caspase-3 pathway (Dang et al., 2015). Curcumin also exerts sensitizer role against cisplatin induced cells such as SiHa and SiHaR killing by modulating of multi drug resistant

proteins like Pgp1 and MRP1, inhibiting HDACs, HPV expression and enhancing acetylation and up-regulating p53. It also causes cell cycle capture at G1-S phase, up-regulates the pRb, p21, p27, and inhibits the cyclin D1 and CDK4. Moreover, curcumin was lowered the cisplatin resistance in SiHaR due to overexpression of MRP1 and Pgp1. Theinhibition of MRP1 and Pgp1 after curcumin treatment lead to sensitization of cervical cancer cells (Roy and Mukherjee, 2014).

Uterine cancer

Uterine cancer is the third most common diagnosed cancer and 8th leading cause of death in cancer patients from cancer among women (Jemal et al., 2007). Uterine carcino-sarcoma comprises of two types of cancer cells, is a rare and fast-growing form of uterine cancer that is the unusual feature of this disease. The response and outlook of patients is poor and they generally do not respond well to chemotherapy when the disease has spread at advance stage. Numerous single-agent chemotherapeutic regimens have been stated to have 10–40% response rate in various clinical trials, for instance; those based on ifosfamide, cisplatin, and paclitaxel. Therefore, to attain higher response rates newer combination of these and other regimens are being tested in several clinical studies. In a phase III clinical trial, a combination regimen is provided, i.e., of ifosfamide and paclitaxel to the women cancer patients with disseminated carcinosarcoma of the uterus as treatment therapy and a significant improvement in survival has been reported. However, the authors suggested that there is a still need to develop the new active agents to further improve the overall survival rates of the disease (Homesley et al., 2007). Cucurmin has the potential to affect multiple targets to prevent and treat the cancer, thus on the basis of this ability many researchers are putting their efforts to use the cucurmin in combination with other active agents in chemotherapy for uterine cancer to speculate its anticancer effects. Conversely, only a small number of studies reported cucurmin's anticancer activity against uterine cancer. Only a few studies reported the ability of cucurmin to induce apoptosis in vitro by the downregulation of Bcl-2 and Ets-1 expression (Yu and Shah, 2007) in cells of endometrial cancer (Wei et al., 2004).

Curcumin potently inhibited SKN and SK-UT-1 cells of uterine leiomyosarcoma (LMS) proliferation in a dose-dependent manner via curcumin inducing autophagy and apoptosis, and enhancing extracellular signal-regulated kinase 1/2 activity (Li et al., 2014). Curcumin application also lowers the uterine LMS cell proliferation by targeting the AKT-mTOR pathway, whereas reduces SKN cell proliferation by inhibiting S6 phosphorylation, and inducing apoptosis. It also suppresses the mTOR, p70S6, and S6 phosphorylation. Curcumin enhances the DNA fragmentation and induces apoptosis in SKN cells (Kondo et al., 2013; Wong et al., 2011).

Ovarian cancer

Ovarian cancer is generally diagnosed in women (Jemal et al., 2007). Diagnosis of ovarian cancer at early stage has a good prognosis and recovery as compared to the advanced stage at which more degeneration occur and less chances of recovery despite of optimal prime therapy in majority of patients (Burger et al., 2007). The treatment of many recurrent diseases like cancer focuses on providing the symptomatic treatment, triggering tumor regression, prioritizing palliative care and improving the quality of life. Over the past decade, the investigations of many researchers and scientist have explored that cucurmin the active ingredient from turmeric had curative effects in ovarian cancer (Guo and Xu, 2005; Nakagawa-Goto et al., 2007). It was also found to inhibit the activation of allied gene products and NF-jB (Li-duan et al., 2006; Liduan et al., 2004; Zheng et al., 2002). Moreover, cucurmin enhances the apoptosis by triggering cells' both intrinsic and extrinsic pathways and by increasing the sensitivity of ovarian cancer cells that show resistance to chemotherapy against standard chemotherapeutic agents (Wahl et al., 2007). Cucurmin (500 mg/kg/day) leads to increase in apoptotic activity of tumor cells, reductions in growth of tumor up to 49–55% and micro vessel density of normal ovarian tumor cells. In these normal ovarian tumors the effect of both cucurmin and docetaxel was decreased. In the second part of this study reduction in tumor growth was investigated in mice with ovarian tumors, i.e., multidrug resistant tumors provided cucurmin and docetaxel treatment. The results show a significant reduction in growth of tumor up to 47% with cucurmin alone and 58% when cucurmin was combined with docetaxel (Lin et al., 2007).

Signal transducer and activator of transcription (STAT) is a family of proteins that have the ability to work both as transcription factors and signal transducers like Signal transducer and activator of transcription-3 (STAT-3). This STAT-3 integrates the signals from kinase pathways and assorted extracellular stimuli and it controls the genes expression and activity particularly that are involved in various vital cellular processes. In numerous cancers like endometrial and ovarian cancer it has been found that STAT-3 has a great constitutive activation (Bowman et al., 2000; Bromberg, 2000). This constitutive signaling of STAT-3 plays a part in oncogenesis by mediating immune evasion, promoting angiogenesis, stimulating cell proliferation and providing resistance to apoptosis that is persuaded by the conventional treatments (Levy and Darnell, 2002).

STAT-3 provides a prospect for therapeutic intervention and also adds directly to malignant behavior of tumor when it is activated in malignancy. STAT-3 is commonly present in normal body tissues in its inactive form, i.e., inactive monomers in the cytoplasm of all body cells and it is activated when phosphorylation of tyrosine occur. This tyrosine phosphorylation converts the inactive STAT-3 molecules to activated form, i.e., change the inactive molecules to homodimer or heterodimer molecules. This activated form of STAT-3 molecules the dimer form can now enter into the nucleus of cell from cytoplasm and stimulate the transcription of several genes (Levy and Darnell, 2002). The transitory activation of STAT-3 molecules in normal body cells is controlled by a group of signaling proteins that inactivate it, for instance; the cascades, suppressors of cytokine signaling proteins (SOCS), protein inhibitors of activated STATs (PIAS) and SH2-containing tyrosine phosphatase (SHP1 and SHP2). The STAT's activity is controlled by a family of proteins, i.e., PIAS family of proteins which includes PIASx, PIASy, PIAS1, and PIAS3. PIAS-1 binds activated STAT-1 and

PIAS-3 binds activated STAT-3 and hinder their ability to bind to DNA when cytokines are stimulated ((Shuai and Liu, 2005). This PIAS-3 is linked with apoptosis in cells of prostate cancer, and found to be highly expressed in many of the human cancers like breast, lung and brain tumors and causes the reduction of growth in cells of human lung cancer (Ogata et al., 2006; Wible et al., 2002). SOCS suppresses the cytokine signaling proteins is another cluster of proteins that have been linked to the regulation of JAK-STAT signaling via negative feedback regulation (Starr and Hilton, 1999). These proteins block the STATs by inactivating JAKs hindering the STATs to bind to receptor binding sites hence blocking its activity. These SOCS also blocks the sites of STAT binding on the activated receptors by STAT inhibitors that are cytokine-induced leads to blocking the STAT-receptor binding. Other key regulators of cytokine signaling are protein tyrosine phosphatases (PTPases) like SHP-1 and SHP-2 domains containing PTPases and Src homology 2 (SH2). These SHP-1 and SHP-2 play crucial roles in the regulation of cytokine signaling, for instance; at N terminus these contain two SH2 domains and at the C terminus contain a catalytic domain, i.e., PTPase which catalyze the JAKs and other proteins of cell by tyrosine dephosphorylation (Jiao et al., 1996). Presently there is a growing interest to investigate a number of natural agents for their preventive and therapeutic potential against cancer. Cucurmin (diferuloylmethane) is one of the natural agents generally used in Asian cuisine, commonly known as turmeric (Shishodia, 2005). Cucurmin is broadly renowned for its anti-microbial, anti-inflammatory and wound healing activities (Aggarwal et al., 2006). Currently, it has been aroused as one of the most auspicious and significant chemotherapeutic and chemo-preventive agents due to its comparatively low- or non-cytotoxicity (Aggarwal et al., 2006). It also has the potential to inhibiting *in vitro* proliferation and propagation of a number of tumor cells, enhances the apoptosis and suppressing the formation of tumors *in vivo* in certain animal models (Karunagaran et al., 2005). While the targets and molecular mechanism of cucurmin action are renowned and a number of studies and reports show that cucurmin suppresses the activity of STAT-3 (Rajasingh et al., 2006). This is the first study that explores the activities and effects of Cucurmin in endometrial and ovarian cancer cells on the negative controllers of activated STAT-3 like SHP-1, SHP-2, SOCS and PIAS (Saydmohammed et al., 2010).

Prostate cancer

In prostate cancer patients the degradation of basement membrane, extracellular matrix (ECM) and metastasize leads to the majority of the deaths in these patients. The numerous components of the extracellular matrix are degraded by the matrix metalloproteinases (MMPs). These MMPs are composed of endopeptidases which are zinc-dependent, i.e., MMP-2 and MMP-9 (Yallapu et al., 2014; Yu et al., 1997). The prime constituent of the cell's basement membrane is the Type IV collagen which is degraded by these metalloproteinases. These MMPs also have been involved in the angiogenesis, tumor cell's metastasis and in the invasion (John and Tuszynski, 2001). Previous investigations showed that a close association among progression of tumor cells and expression of metalloproteinases on the prostate cancer cells in humans existed (Trudel et al., 2004).

In earlier period, for the prevention and treatment of cancer especially prostate cancer, phytochemicals from fruits and vegetables have been used (Clark et al., 1996; Yip et al., 1999; Zhang et al., 2004). Among these, cucurmin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione) is the main ingredient and exerts apheliotropic effects on the cancer cells of prostate (Adams et al., 2005; Nakamura et al., 2002; Valentini et al., 2009). Cucurmin was also used to determine its effects to induce apoptosis in the cancer cells which is linked with the activation of enzyme in the apoptotic cascade that is caspase-3 enzyme (Mukhopadhyay et al., 2001). In an-other study the effects of Cucurmin was investigated in both *in vivo* and *in vitro* tests against metalloproteinases, i.e., MMP-2 and MMP-9. The results clearly showed that there was a significant inhibition of MMP-9 than MMP-2 in both tests. In murine prostate cancer cells the hematogenous metastasis has been affected by the expression of these MMP-9 (Sehgal et al., 1998)). Therefore, cucurmin by decreasing these MMPs particularly by reducing the activity of MMP-9 helps to prevent the pulmonary metastasis (Guo et al., 2015).

The cucurmin show its anti-cancer effects by inducing the apoptosis in some cancer cell lines and by blocking the cell cycle at specific stages. In case of blocking the cell cycle stages the Cucurmin has been investigated and described to block the cells in cell cycle at all the stages in which the most common type of block is G2/M block (Holy, 2002; Lin et al., 2009). Furthermore, the cucurmin remarkably trigger the apoptosis in some cell types and seems to exert a range of effects on inducing and promoting the cell death which depends on cell line (Ranjan et al., 1999) while it inhibit apoptosis in others (Sikora et al., 1997). The molecular mechanisms exhibited by the cucurmin are beginning to be revealed, i.e., the cucurmin action to induce apoptosis, effects on transcription factors, inhibition of NFkB and nitric oxide production and affects a number of signaling pathways (Onoda and Inano, 2000). It also inhibits c-Fos, c-Jun, and AP-1 activity (Pendurthi et al., 1997) a number of enzyme activities and kinases, i.e., protein kinase C, phosphorylase kinase, EGF receptor (EGF-R), erbB2, and ornithine decarboxylase (Korutla and Kumar, 1994). Cucurmin also affects a number of cell cycle protein's expression on the cells; these proteins are ras, $p34^{cdc2}$, thymidine kinase, PCNA, cyclin E, p21 and Ki67 (Chuang et al., 2000). Additionally it also change the expression of proteins which are apoptosis related like p53, Bcl-2, and Bax (Anto, 2002; Choudhuri et al., 2002).

Cucurmin reported to inhibit the progression of colonic adenocarcinomas which was induced by azoxymethane in rats. In this study cucurmin was administered in the diet at a dose of 0.2% to rats that showed positive results in reducing carcinoma; unrelatedly to the stage of disease whether in the promotion/progression or initiation/postinitiation stage (Kawamori et al., 1999). While at a dietary dose of 0.1% cucurmin, it causes a reduction of 64% in the Min mice in adenoma formation. This adenoma formation wharfs a defect in a gene, i.e., adenomatous polyposis coli gene which is a basic cause of familial adenomatous polyposis in the humans (Mahmoud, 2000). Cucurmin also exhibit the chemo-preventive action because it has a wide range of biological activities, i.e., suppression of NF-kB

activation and inhibition of activity of COX-2 enzyme, formation of reactive oxygen species (ROS), prostaglandin synthesis and expression of the COX-2 enzyme (Reddy and Lokesh, 1994; Singh and Aggarwal, 1995). Considering the chemo-preventive actions of cucurmin at both stages of tumor formation and tumor proliferation it induces and triggers the apoptosis in these tumor cells; this apoptosis is induced in a concentration-dependent mode (Samaha et al., 1997). It has been revealed that cucurmin also has the potential to inhibit the c-erb2/neu function and EGF-receptor (Hong et al., 1999). From these studies it is indicated that cucurmin can function as a chemo-preventive agent as well as therapeutic agent because it has a potential to prevent and treat pre-existing neoplasms especially prostate cancer by inhibiting the COX-2 enzyme activity and tyrosine kinases activity. Cucurmin also exhibit the potential to certainly suppress the growth of prostate cancer cells and noticeable inhibition of angiogenesis in vivo in the later part of this study. In this work tumor cells was implanted heterotopically and grow in nude mice by using LNCaP prostate cancer cells. These results clearly infer that in pharmacological doses the cucurmin has the potential to inhibit the development of prostate cancer and to treat this cancer by snooping with numerous receptor pathways, i.e., growth factor receptor pathways like VEGF-R and EGFR pathways (Dorai et al., 2001). This cancer is prevented up to its hormone refractory state. Currently, nano encapsulated formulations of cucurmin are being investigated to treat prostate cancer. These nanoformulations e.g. curcumin loaded cellulose nanoparticles (cellulose-CUR) ensure improved bioavailability and better anti-cancer efficacy compared to free cucurmin (Yallapu et al., 2014)).

The genesis and metastatic progression of prostate cancer are linked with the inhibitor of DNA binding 1 (Id1). Curcumin lowers the cell viability, induces apoptotic death, effectively lowered the expressions of mRNA and Id1 in a dose-dependent manner in PC3 cells. It also enhances the protein expressions of p21 and also arrests the both S and G2/M phases of PC3 cells (Chen et al., 2014; Eom et al., 2015). Recently, (Lee et al., 2015) determined that treatment of curcumin significantly induced apoptotic death, triggered extensive cytoplasmic vacuolation, up regulated the ER hassle markers CHOP and Bip/GRP78 and induced ER stress by triggering ROS generation. Additionally, it lowere cancer growth by inducing ROS production followed by vacuolation-mediated cell death.

Curcumin reduced the protein expression of MUC1-C and NF-κB subunit p65, which were abrogated in the presence of the inhibitors of MEK/ERK1/2 (PD98059) and SAPK/JNK (SP60015). Curcumin inhibits the growth of androgen-independent prostate cancer cells through ERK1/2- and SAPK/JNK-mediated inhibition of p65, followed by reducing expression of MUC1-C protein (Li et al., 2014). It also inhibits nuclear β-catenin, AR expression, STAT3 and AKT phosphorylation and suppression of Bcl-xL, Mcl-1 proteins, and caused induction of PARP cleavage. Furthermore, curcumin down regulates the oncogenic miR21 and up-regulates the miR-205 (Yallapu et al., 2014). In another study conducted by Wang et al. (2015), curcumin (1μM) suppresses the LNCaP prostate cancer cells through enhancing cell apoptosis and cell cycle capture of G0/G1 phase, increasing the ratio of Bax to Bcl-2 proteins, decreasing the activation of NFκB, PI3K/Akt and Stat3 pathways, respectively. Similarly, Guo et al. (2015) explored the cytotoxic role of curcumin (0.2 to 0.8 μmol/l) suppressed the PC cells via increasing cell cycle suppressor CDKN1A at protein levels, regulating the translation of CDKN1A, as well as inhibiting the miR-208, and suppressing growth of PC via miR-208-mediated (Guo et al., 2015).

Head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) comprised of a heterogeneous group of tumors includes the oral cavity, hypopharynx, nasopharynx, oropharynx, larynx and face. Moreover, different types of therapies such as radiation therapy andchemotherapy have been using for patients with HNSCC (Aggarwal et al., 2003; Wilken et al., 2011). From last decade, people are more diverting towards the consumption of natural sources due to strong anticancer properties against (HNSCC). Among these, Cucurmin from turmeric has been revealed to suppress cellular proliferation in oral, colon, breast and other cancers (ElAttar and Virji, 1999). Nuclear factor causes the activation of various cell processes like apoptosis and cell growth (Schmitz et al., 2004). This factor is activated in many cells such as inflammatory cytokines, i.e., tumor necrosis factor (TNF) and interleukin-1 and mitogens (Aggarwal et al., 2003; Duarte et al., 2010). Therefore, NF-nh increased the transcription of growth-stimulating genes like Bcl-2, COX2 and cyclin D1 and it is key cell cycle regulator. Cucurmin play a key role in the down-regulation of NF-nB (Kim et al., 2011a). Cucurmin *in vivo* and *in vitro* suppresses growth of HNSCC and inhibits the activity of NF-nB this hypothesis is tested many times. It has various hypothesized actions like suppression of the cell cycle, stimulation of apoptosis through mitochondrial-independent and mitochondrial-dependent pathways and inhibition of proliferation that is induced by growth factors (Morin et al., 2001; Mukhopadhyay et al., 2001). It is observed that addition of Cucurmin decreased the activation of NF-nB and the expression of cyclin D1 (Jee et al., 1998). This NF-nB is one of the key activators of transcription. By inhibiting the phosphorylation of InB the activation of NF-nB is occurred and it is the one of the main mechanisms of NF-nB activation; this causes the retention of NF-nB in the cytoplasm (Piwocka et al., 1999). TNF-h enhances InB phosphorylation and is a key stimulatory factor of NF-kB activation. On the other hand, cucurmin reduces the activation of NF-nB by preventing this phosphorylation. This effect of cucurmin is supported by this study in HNSCC via inhibition of the NF-nB pathway and its effect in cell cycle regulation because it reduces the cyclin D1 expression in addition to inhibition of NF-nB activation (Anto, 2002).

Curcumin shows anticancer activity in FaDu (hypopharyngeal) and Cal27 (tongue) HNSCC cell lines such as up regulation of pro-apoptotic Bik, down-regulation of survival signaling by AKT and NF-κB prior to the induction of the caspase-cascade reduction of cell proliferation. These mechanisms are associated with cell death (Xi et al., 2015). Moreover, Amin et al. (2015) determined that curcumin prevented from head and neck cancer through several such as inhibition of p-AKT, induction of p73 and Bcl-2, induction of p53 and the related protein p73 in neck and head cancer cell lines.

Curcumin as an anticancer agent, it enhances the the Bax/Bcl-2 ratio, PARP-1 cleavage, the expression of LC3 II, and the suppression of ERK1 and ERK2 phosphorylation, simultaneously with the formation of autophagic vacuoles. It induces cytoplasmic NF-κB accumulation, reduces the growth of transplanted salivary gland cancer cells (SALTO) in BALB/c mice (Masuelli et al., 2014). Moreover, it also increases the levels of phosphorylated IκBα, and lowers the levels of phosphorylated IKKβ and phosphorylated p65. It also inhibits NF-κB p65 phosphorylation by PKAc (Zhu et al., 2013). Curcumin has significant reduction in IKKβ kinase activity of head neck squamous cell carcinoma (HNSCC) cell lines. It also reduced IFN-γ, IL-2, IL-8, IL-10, IL-12p70, and clustered together, and granulocyte macrophage colony stimulating factor and TNF-α expression in both the salivary supernatant and salivary cells (Kim et al., 2011b). Curcumin exerted anti-proliferative effect against NF-κB factor, and downstream gene products such as Cyclin D1, c-myc, Bcl-2, NOS, COX-2, interleukins, TNF-α, and MMP-9, respectively (Wilken et al., 2011). It also reduces the expressions of IκBα, phospho-IκBα, cyclin D1, and IKKβ, lower NFκB activity and also suppresses the cytoplasmic and nuclear IKKβin cisplatin- and curcumin-treated cell lines (Duarte et al., 2010). In a study using In4NQO carcinogenic model *in vivo* and *in vitro*, administration of curcumin (15 mg) blocked the cancer cell migration and invasion via down regulating pS6 linked with a significant reduction in MMP-9. It also blocked the nicotine-induced activation of the AKT/MTOR pathway to prevent from the nicotine adverse effects (Clark, 1996). Curcumin suppresses SCC-1, SCC-9, A431 as well as KB, cell lines in HNSCC. Curcumin lowers COX-2 expression and inhibits the phosphorylation of EGFR in SCC-1 cells. Similarly, it lowers the tumor weight and tumor size in tumor-bearing mice as well as also enhances the effect of radiation on HNSCC cell growth *in vivo* and *in vitro* (Khafif et al., 2009).

Curcumin has ability to suppress the HNSCC due to reserve of the transcription factor nuclear factor kappa B. Higher doses of curcumin exhibited inhibition activity against CAL27, CCL23, UM-SCC1, UM-SCC14A, IL-6 and IL-8 levels in HNSCC via inhibiting the IL-6 and IL-8 in all cell lines in dose-dependent manner (Cohen et al., 2009). In HNSCC cancer cell lines, the suppressed STAT3 phosphorylation and nuclear translocation of STAT3 are suppressed by the administration of curcumin in a time and dose dependent manner as well as also abrogated the IL-6-induced activation of STAT3 (Chakravarti et al., 2006). Moreover, curcumin also triggers cell death in HNSCC cell lines UM-SCC1, CCL 23, and CAL 27 in a dose-dependent fashion through lowering nuclear expression of NF-kappabeta activated protein, and lowering cyclin D1 (LoTempio, 2005).

Breast cancer

Recently, there has been a growing interest to explore the potential effects of naturally occurring compounds for the treatment of breast cancer and they are recognized for it. Among plant-derived polyphenols, cucurmin found in turmeric rhizome is a phytochemical, used in Indian cooking as a spice, flavoring and coloring agent (Lin and Lin-Shiau, 2001). Epidemiological evidences and studies suggested that the risk of developing several types of cancer, as well as breast cancer decreased by the consumption of foods that have high levels of cucurmin (Al-Hujaily et al., 2010). This theory that cancer incidence decreased by the consumption of cucurmin is supported by the results from various experimental studies. Cucurmin *in vitro* not only inhibit the growth of a number of human cancer cells lines as well as estrogen receptor negative (ERa-) cells of human breast cancer (Chisholm et al., 2004; Thangapazham et al., 2007), but also enhances the anticancer effects of other compounds like Trichostatin A (Yan, 2013). It also induces the apoptosis by arresting the cell cycle at G1/G0 and G2/M-phase, respectively because of having the cytotoxic effects (Lin et al., 2009). Similarly, it also has the potential to inhibit the cyclins and cyclin dependent kinases, Nuclear factor-kappa B (NF-kappa B), transcription factor and subsequently numerous NF-kappa B-regulated gene products (Masuelli et al., 2014; Aggarwal et al., 2007; Aggarwal et al., 2006; Mukhopadhyay et al., 2002). Moreover, numerous *in vivo* studies have revealed the fact that consumption of cucurmin decreases tumor initiation and growth (Inano and Onoda, 2002). Cucurmin in combination with MCF-7 when provided as treatment to cells of human breast cancer leads to synergistic growth inhibition of these cancer cells whereas in an orthotopic model Cucurmin decreased the volume of pancreatic tumor (Kunnumakkara et al., 2007). Additionally, the cucurmin by arresting the cell cycle at S/G2M stage synergistically hinders the growth of oral epithelial cells of humans. Furthermore, reports indicate that cucurmin inhibits the expression of c-myc, c-jun and c-fos proto-oncogenes (Roy et al., 2011). In a latest study, Singh and Aggarwal (1995) indicated that cucurmin via convergence of several stimuli inhibits the activation pathway of transcription factor NF- kB that was mediated by protein kinase, protein tyrosine kinase and ubiquitin conjugation enzymes (Bimonte et al., 2013).

Telomerase is an enzyme that provides karyotype stability, adds to telomeres nucleotide repeats and compensates the loss of DNA that take place through replication. As cells divide, telomeres shorten in the absence of telomerase until senescence occurs (Kim et al., 2012). Studies have showed that in tumorogenesis the telomere stabilization and the telomerase enzyme activation is important necessary steps (Buys, 2000). The activity of telomerase enzyme is generally suppressed in somatic cells however its activity is reactivated in most human cancer cells and immortal cells. Human telomerase enzyme is comprised of two main components an RNA (hTER) and catalytic subunit; RNA component works as template for the simple sequence and catalytic subunit acts as reverse transcriptase (hTERT). In recent times two protein components, hTEP-1 and hEST-2 have been identified these protein components display an association with telomerase activity (Beattie et al., 1998). Telomerase activity in tumors has been closely coincides with the expression of hTERT mRNA, however the hTEP-1 and hTER template are expressed constitutively and these proteins have association with telomerase (Calaf, 2012). Thus, at the level of stability of hTERT mRNA or transcription the activation of telomerase is regulated as a part of this process. The activity of telomerase is shut down when positive cells of telomerase are exposed to differentiating agents, i.e., protein kinase C inhibitors or c-myc antisense oligonucleotides (Fujimoto and Takahashi, 1997). It is also reported by many studies that

telomerase is activated by c-myc oncogene expression via up-regulating the mRNA that encodes the catalytic subunit of telomerase, hTERT (Al-Hujaily et al., 2010).

Cucurmin has a potential to inhibit mutagenesis and carcinogenesis induced chemically in many animal tumor models tumor models (Kawamori et al., 1999). Cucurmin regulates a number of cellular processes like inhibition of protein kinase C activity, NF-kB activity, intrinsic kinase activity of epidermal growth factor (EGF) receptor, nitric oxide synthetase activity, lipid peroxidation, and production of reactive oxygen species (Calaf et al., 2011). Moreover, Cucurmin inhibits the expression of c-myc, c-fos and c-jun proto-oncogenes (Zhou et al., 2009). It is also documented that Cucurmin inhibits the replication of human immunodeficiency virus- type I (HIV-1) thru down-regulating the long-terminal repeat (LTR) that is directed by expression of p24 gene. In a current study (Labbozzetta et al., 2009; Ramachandran and You, 1999), cucurmin displayed a great potential to significantly induce the apoptosis in breast cancer cells (MCF-7/TH) that show resistance to many drugs, however when the same concentration of cucurmin provided to mammary epithelial cells (MCF-10A) of humans it causes an insignificant level of apoptosis. Cucurmin also has chemo-preventive action as it down-regulates mutant p53 mRNAs, PCNA and Ki67 in breast cancer cells (Ramachandran and You, 1999).

Mohankumar et al. (2014) determined that curcumin (30 μM) inhibited MCF-7 cell lines through modulating the apoptotic markers (intrinsic pathway: Bcl-2, p53, cyt c, Bax, caspase-9, 3, Apaf-1, PARP; extrinsic pathway: caspase 8, FasL). Curcumin shows anticancer role in MCF-7 cell lines through inducing the apoptosis of regulatory protein Bcl-2, decreasing Bax expression and strongly inhibiting the paclitaxel-induced activities of EGFR signaling (Zhan et al., 2013; Zhou et al., 2014). The over expression of Flap endonuclease 1 (Fen1) is associated with breast cancer. Curcumin treatment suppresses the Fen1 dependent propagation of MCF-7 cells, significantly induces Nrf2 protein expression, and inhibits Fen1 protein expression. It could lead to Nrf2 translocation from the cytoplasm to the nucleus and decrease Fen1 promoter activity by declining the recruitment of Nrf2 to the Fen1 promoter (Chen et al., 2014). Recently, Akkoç et al. (2015) has been found the anti-breast cancer role in MCF-7 cell lines through triggering intrinsic apoptotic cell death, activating mitochondrial permeabilization, altering pro- and anti-apoptotic Bcl-2 expressions, modulating the expression of Bcl-2, and autophagosome formation.

Bisphenol A (BPA) is known as endocrine disrupter and promote the development of breast cancer. Curcumin suppresses the prolifertive effects of MCF-7 induced by BPA. Curcumin reversed the oncogenic miR-19a and miR-19b dysregulated expression and upregulation of miR-19-related downstream proteins, such as p-AKT, PTEN, p53, p-MDM2, and proliferating cell nuclear antigen induced by BPA. It also exhibits shielding effects against BPA associated breast cancer promotion by modulating miR-19/PTEN/AKT/p53 (Li et al., 2014). Curcumin suppresses the NF-κB promoter action and caspase 3/7 dependent apoptosis in a dose dependent way (Mezzanotte et al., 2014). Kang et al. (2014) determined that curcumin reversed several changes in MCF-7 cells such as intemperance in mitochondrial membrane potential ($\Delta\psi$m), blocked curcumin-mediated Bax up-regulation, p21 up-regulation, Bcl-2 down-regulation, G2/M arrest cell cycle, and caspase-3 activation. Recently, Chung and Vadgama (2015) determined the potential effect of curcumin (10 μM) against 2 breast cancer cell lines (MDA-MB-231 cells and MCF7 cells transfected with HER2) by decreasing the cancer stem like Cluster of differentiation 44 (CD44)-positive cell population. ITG β4 palmitoylation is accompanied with the proliferation of breast cancer cell lines whereas curcumin administration effectively suppressed the ITG β4 palmitoylation, palmitoylation independent of growth factor induced phosphorylation of key ITG β4 Ser and Tyr residues, and blocked autoacylation of the palmitoyl acyltransferase (Mezzanotte et al., 2014). The mammary carcinoma cells are associated with retinoic acid by expressing high levels of fatty acid-binding protein 5 (FABP5). This protein caused the making of peroxisome proliferator-activated receptor β/δ (PPARβ/δ) via delivering retinoic acid. A study conducted by curcumin reduced the FABP5 and PPARβ/δ expressions, suppressing p65 (transcription factor), suppressed PPARβ/δ target genes, VEGF-A and PDK1. It also activates the caspase dependent apoptotic signing pathways and the increases the cellular assimilation and inhibting P-glycoprotein (P-gp) pump function in resistant MCF-7 cells (Wang et al., 2015). Similarly, group of researchers (Shiri et al., 2015) determined that expression of miR181b modulated by curcumin treatment in metastatic breast cancer cells. Interestingly, miR181b down-modulates CXCL1 and -2 through a direct binding to their 3′-UTR. Overexpression or inhibition of miR181b in metastatic breast cancer cells has a significant impact on CXCL1 and -2. Importantly, in metastatic breast cancer cells, over-expression of miR181b inhibits metastasis formation *in vivo* in immunodeficient mice. It up-regulates miR181b and down-regulates CXCL1 and -2 in cells (Farhangi et al., 2015; Kronski et al., 2014). It also lowers the STAT3, IL-10 and arginase I gene expression in twenty-seven BALB/c mice.

Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) produces DNA adduct and DNA strand breaks and reported as food carcinogen. Curcumin has anticancer potential against PhIP-induced cytotoxicity in normal breast epithelial cells (MCF-10A). Curcumin has potential to protect from the breast ca ncer through suppressing PhIP induced DNA adduct creation and DNA double stand breaks with a concomitant lowering in ROS (reactive oxygen species) production. It also suppresses the caspase-3 and -9 with a consequent inhibition of cell death (Jain et al., 2015). Numerous researchers, (Charpentier et al., 2013; Chen et al., 2014) determined that curcumin reversed doxorubicin-induced morphological changes, inhibited doxorubicin-induced upregulation of vimentin expression, and inhibited doxorubicin-induced downregulation of E-cadherin expressions. It also suppressed doxorubicin-induced EMT by inhibiting the TGF-β and PI3K/AKT signaling pathways in Triple-negative breast cancer (TNBC) cells.

Pulmonary and lung cancer

Dose-dependent pulmonary fibrosis is caused by an anti-tumor antibiotic Bleomycin (BLM) that displays presence of macrophages in alveoli described as alveolar macrophages (AM),

eosinophils and neutrophils inside the alveolar structures (Ito et al., 2012). These activated alveolar macrophages secrete tumor necrosis factor-a (TNF-α) which show a strong association with pathogenesis of pulmonary fibrosis (Zhang et al., 1993). Meanwhile, the body's defense mechanism secrete anti-TNF antibody which was revealed to inhibit the BLM-induced pulmonary fibrosis (Piguet, 1989a; Piguet, 1989b). In addition to increased macrophages, eosinophils and neutrophils in pulmonary fibrosis linked with BLM treatment there has been also an increased levels of reactive oxygen and nitrogen species that are toxic which are produced by the infiltrating inflammatory cells of lungs (Yamazaki et al., 1998). Therefore, the active agents that reduce this oxidative stress have potential clinical value and protective effects against pulmonary fibrosis induced by BLM.

Cucurmin in BALF decreases the total cell numbers by inhibiting the movement of inflammatory cells to the inflammation site through epithelial and endothelial basement membrane. This may be due to the cucurmin-mediated membrane stabilization that is a property of Cucurmin (Nirmala and Puvanakrishnan, 1996). Currently, there has been increased concern to reveal the potential effect of cucurmin, few of these studies shown to inhibit the production of several cytokines and chemokines including TNF- α through monocytes and alveolar macrophages by cucurmin (Abe et al., 1999). Cucurmin also plays a protective role in development and treatment of BLM-induced pulmonary fibrosis because it blocks the release of cytotoxic free radicals, and TNF-α and by scavenging the free radicals (Gescher et al., 1998). A great reduction in the release of TNF-a by activated macrophages in BLM-induced pulmonary fibrosis was seen in cucurmin treatment. These findings about the potential of cucurmin against pulmonary fibrosis and reduction in production of inflammatory chemokines and cytokines including TNF-α by means of monocytes and alveolar macrophages are consistent with earlier reports (Abe et al., 1999). As the cucurmin block the initiation and development of inflammatory response that is induced by BLM via suppressing the release of TNF-α through activated macrophages, it inhibits the recruitment of inflammatory cells and modifies the expression of adhesion moieties on both endothelial cells and leukocytes. Supporting this argument, cucurmin has been described to inhibit the expression of adhesion moieties that are induced by TNF-α on endothelial cells of human umbilical vein (Kumar et al., 1998).

Small cell lung cancer (SCLC) represents a highly malignant and aggressive form of cancer associated with early metastasis and poor prognosis. Curcumin has been reported to suppress the STAT3 phosphorylation which results in inhibition of proliferation, cell cycle, migration, invasion and angiogenesis of SCLC cells (Yang, 2013). Curcumin inhibits proliferation of tumors in NSCLC via activating cancer suppressor DnaJ-like heat shock protein 40 (HLJ1), inducing G0/G1 phase arrest, suppressing the MTA1 expression, and inactivating Wnt/β-catenin pathway (Lu et al., 1993). A group of researchers (Xu et al., 2014; Zhou et al., 2015) evaluated the anticancer role of curcumin on A549 and H1299 lung cancer cells. It suppressed the cell growth, enhanced the [Ca2+]i level and induced the apoptosis as well as also downregulated the expression of Bcl-2, and elevated the phosphorylation level of IP3Rin a concentration-dependent manner. The group of researchers (Chen et al., 2014) determined that curcumin (10 μM and 20 μM) treated to NSCLC 95D cells and showed significant anti-proliferative role, by steering the crosstalk between the adherents junction and Wnt signaling pathway via EGR-1. Similarly, it also inhibits the overexpression of MMP-9, lowers the expression of PKCα, Nox-2phosphorylated ATF-2, and P47phox, as well as intracellular ROS generation. Curcumin also modulates the activation of the PKCα/Nox-2/ROS/ATF-2 pathway to inhibit cell invasiveness in A549 cells in a dose dependent manner (Fan et al., 2015). Similarly, curcumin increased the inhibitory activity of cisplatin (DDP) and promoted the DDP-induced apoptosis in A549/DDP cells (DDP-resistant lung adenocarcinoma cells). It also down regulated the DDP-induced FANCD2 monoubiquitination and nuclear foci formation which are the FA/BRCA pathway DNA injury repair processes. In resulting, curcumin increased the sensitivity to DDP in A549/DDP cells through the suppression of FA/BRCA pathway and reversed the cisplatin resistance of A549/DDP cells (Chen et al., 2014).

The miR-192-5p/215 expressions were promoted in in A549 cells, H460, and A427 cells with the treatment of curcumin. It also induced apoptosis which is mainly depend on miR-192-5p/215 induction, and antagonizing miR-192-5p/215 expressions lung cancer cell lines (Wu et al., 2015; Ye et al., 2015). Furthermore, curcumin has anticancer effect on NCI-H460 human lung cancer cells over multiple mechanisms such as (1) induction of apoptosis, (2) cell morphological changes, (3) lower viable NCI-H460 cells, (4) promotion of ROS and Ca^{2+} production, (5) reduction in level of $\Delta\Psi$m, (6) activation of caspase-3, -8 and -9, (7) up regulation of Endo G, AIF, PARP, and Fas ligand (Fas L), andFas levels, and (8) promotion of expression of ER stress-associated proteins such as GADD153, GRP78, ATF-6α, IRE1β, ATF-6β and caspase-4, respectively (Ko et al., 2015; Liu et al., 2015). Likewise, neutrophil elastase (NE) led to angiogenesis in lung cancer cells by stimulating inflammation. Curcumin prevented from lung cancer development in inbred C57BL/6 rats through regulation of the HIF1α/mTOR/VEGF/VEGFR cascade pathway. It also reversed the changes in angiogenesis through lowering NE excretion and stimulating α1-antitrypsin (α1-AT) then insulin receptor substrate-1 (IRS-1) production.

It also influenced the endothelial cells (EC) tube formation in dose dependent manner (Fan et al., 2015). It can be an effective to treat solid organ tumors via regulating oncogenes like egr-1, p53, bcl-XL, c-myc, etc. protein kinases like MAPK; and enzymes like COX and LOX, and transcription factors like STAT-3, NF-kB, and AP-1; respectively (Mehta et al., 2014). Similarly, Chen et al. (2014) determined that administration of curcumin (10 μM) effectively suppressed the transforming growth factor β1in, inhibited migration and invasion, inhibition of PAK1/Rac1 signaling pathway and MMP-9 and MMP-2 expression. Similarly, Lev-Ari et al. (2014) explored the therapeutic role of curcumin (0–50 μM) against NSCLC cells via 36% reduction in weight of intra lung tumors, inhibition of COX-2, p65 expression, IkB, and ERK1/2 activity was accompanied with reduced survival and increased induction of apoptosis.

Stomach or gastric cancer

Recent researches showed that cucurmin applies a number of pharmacological actions in acute gastric mucosal lesion model by reducing potent radical scavenging activity and restricting inducible nitric oxide synthase (iNOS). Rafatullah et al. (1990) anticipated the effect of cucurmin on anti-ulcerogenic mechanism, similarly inhibitory effect on antioxidant activity, cyto-protection, gastric secretion, and prohibition of mast-cell degranulation, need to be assessed again. The basal gastric acid secretion is reduced and it is identified that gastric mucus synthesis were regulated by gastric mucosal constitutive nitric oxide synthase (cNOS) as well as secretion of gastric mucus and gastric mucosal microcirculation (Rastogi et al., 1998). The stimulation of iNOS activity is due to the overproduction of nitric oxide by leukocytes and it is observed that in pylorus-ligated rat it causes the decrease of gastric acid secretion and encouraging gastric lesions on ischemia-reperfusion (Tanaka et al., 2001). In rats lesion formations were prevented when treated with selective iNOS inhibitor (aminoguanidine), however the gastric acid production enhances that is reduced by decreased ischemia-reperfusion (Das and Das, 2002). Researches carried earlier supports that the antiulcerogenic effect was partially dissipate through the 40 mg/kg dose of cucurmin as it upsurge acid production. The free radicals formed in the incidence of excessive NO accomplished from the stimulation of iNOS activity and superoxide radicals were hydroxyl radical, superoxide radical and cytotoxic peroxynitrite compound that produce gastric lesions. The cimetidine has gastroprotective effect and its action is independent on gastric acid secretion, and is also linked with its activity in scavenging hydroxyl radical and to tissues it is more toxic and reactive than superoxide radical (Uchida and Kawakishi, 1990). Cucurmin is not an effective hydroxyl or superoxide radical but it has been observed that it is more efficient nitric oxide scavengerand singlet oxygen quencherm (Sreejayan and Rao, 1997). Subsequently, it has been also testified that that cucurmin dose of less than 50 mg/kg body weight stimulates mucin secretion and subdues the stimulation of iNOS activity (Chan et al., 1998), it is susceptible that that at dose less than 40 mg/kg of cucurmin shows anticipatory effect and it is because of direct upsurge in mucin secretion, and the antioxidant property exhibit as nitric oxide scavenger and as singlet oxygen quencher and also counting it's iNOS inhibitor property. In acetic acid-induced ulcer the oral dose of cucurmin of 20–80 mg/kg/day demonstrate significant healing-promoting effect along with the improvement in the mucosal layer regeneration (Sidhu et al., 1998).

The human chronic gastric ulcer and the model of chronic gastric ulcer prompted by the topical application of acetic acid in rat resemble both grossly and histologically (Szabo and Vincze, 2000). It has been advised that in the healing process of formed ulcer, the factors that contribute includes neovascularization, propagation of mucosal cells, epidermal and transforming growth factors and adequate mucosal blood flow (Ohta et al., 1999). Recently, on the healing ulcers an inhibitory effect was exerted by the oxygen free radicals derived from infiltrated neutrophil, and it has been observed that the in the promotion of ulcer healing process it is required to inhibit the lipid peroxidation in ulcerated tissue or the decrease of neutrophil infiltration into ulcerated tissue (Motilva et al., 1996).

One of the major pathogenic factors that lead to the initiation of gastric ulcer disease is the hypersecretion of gastric acid. The antagonistic damage and vascular leakage caused on the basement membrane of both epithelial and mucosal cells in the gastric wall is due to the back diffusion of acid into the mucosa, ultimately restricting the restoration process in the injured mucosa and encouraging the development of apoptosis to deeper layers of the mucosa (Mishra et al., 2009).

Cucurmin has an effective action against ulcer, it subdue the reproduction of Helicobacter pylori and also protecting against gastric mucosal injury (Zaidi et al., 2009). It does not produce any adverse effect on human health when taken up to a dose of 10g/day and used in clinical trials as considered to be an effective chemo-preventive agent (Aggarwal et al., 2003). Though, Cucurmin is poorly soluble in water, i.e., 11 ng/mL is the maximum solubility in plain aqueous solution. This is the reason it is slightly absorbed in the gastrointestinal tract (Tønnesen et al., 2002). It is observed in rats that the Cucurmin oral bioavailbility is very low only 1%.

Curcumin treatment induced ROS production and apoptosis in BGC-823 cells. It also activated ASK1 which is responsible for phosphorylation of JNK (Liang et al., 2014; Zou et al., 2015). Several researchers (Da et al., 2015; Khan et al., 2015) assessed the effect of different concentrations of curcumin (40, 80, or 160 mg/kg/day) for 56 days weeks on the mice treated with 80 and 160 mg kg-1 day-1 curcumin expressively lowered tumor volume, reduced the expression of podoplanin, Prox-1, VEGFR-3 levels, lymphatic vessel endothelial receptor 1 (LYVE-1), VEGFR-3 mRNA expression, and increased apoptosis rates of tumor cells in a concentration-dependent manner.

Curcumin has preventive role against AGS cells through inducing apoptosis, G2/M arrest, enhancing expression of cyclin B1 and a lowering expression of cyclin D1,enhancing caspase-3, -8, and -9, downregulating of rat sarcoma (Ras) and upregulating of extracellular signal regulated kinase (ERK) were also observed in AGS cells treated with curcumin (Cao et al., 2014). In addition to, curcumin also suppresses the COX-2, β-catenin, and microsomal prostaglandin E synthase 1 activation, macrophage infiltration and STAT3 pathways (Uehara et al., 2014)). It also induces apoptosis in SGC-7901 that linked with the indulgence of MMP (mitochondrial membrane potential) and the release of cytochrome c into the cytosol. In addition to, curcumin down regulates Bcl-2 and up-regulates Bax that led to the cleavage of caspase-3 and enhanced cleaved PARP (Xu et al., 2014).

Liver or hepatic cancer

Curcumin induces cell death and inhibits the NF-kB factor in sensitive lines. The curcumin are linked with depletion of selective CSC, reduction in SP size & sphere formation, down-regulation of CSC markers and suppression of tumorigenicity (Marquardt et al., 2015; Zhao et al., 2015). Curcumin can inhibit propagation of MHCC97H liver cancer cells by inducing apoptosis, stimulating TLR-4/MyD-88 signaling pathway in a concentration dependent manner (Li et al., 2014).

Curcumin could reverse the proliferation and migration of HepG2 cells in hepatocellular carcinoma under CoCl2-induced hypoxia condition, which might be associated with inhibiting

up-regulated expressions of HIF-1alpha protein and EMT (Duan et al., 2014; Webster et al., 2014; Zhou et al., 2014). Preventing role of curcumin against HCC cells are accompanied with suppression of invasion and migration of these cells, reduction the MMP-2 & MMP-9 expressions, and p38 phosphorylation (Liang et al., 2014). Curcumin acts as anti-hepatic cancer through multiple mechanisms such as inhibiting VM, lowering cell migration and MMP9 production, suppressing AKT and STAT3 phosphorylation (Chiablaem et al., 2014). Moreover, curcumin exert anti-proliferative role against MHCC97H liver cancer cells through exciting intracellular ROS \ generation, enhancing intracellular ROS formation, activating the TLR-4/MyD-88 signaling pathway, and caspase-8 and caspase-3 (Li et al., 2014).

Pancreatic cancer

Adenocarcinoma of the pancreas is one of the most overwhelming neo-plastic maladies (Jemal et al., 2002; Tian et al., 2011). During normal homeostasis, nuclear transcription factor-kB (NF-kB) act as an inactive hetero trimer, exist in the cytoplasm and composed of IkB-α, p50 and p65 (Karin and Ben-Neriah, 2000). Proteasome assisted IkB-α after activation and endures it to phosphorylation and ubiquitination-dependent degradation. Subsequently, nuclear localization signals were observed on the p50 to p65 hetero dimer, directing them to bind diverse growth-regulatory genes and nuclear translocation lead to gene transcription. The activation of IαB kinase is interceded by the phosphorylation of IkB-α (Jobin et al., 1999; Li et al., 2011b). The three types of proteins encompasses to form IαB kinase complex, i.e., IKK-β, IKK-α, IKK-γ/NF-kB essential modulator, for phosphorylating IkB-α, the kinases being responsible were IKK-β and IKK-α (Maute et al., 2009; Pahl, 1999). Interleukin-8 (IL-8), IkB-α, and cyclooxygenase-2 (COX-2) are the regulated genes for NF-kB (Glienke et al., 2009; Sahu et al., 2009). The molecules being responsible for the metastatic and proliferative activity in the neoplasm of pancreatic carcinoma cells were IL-8 and COX-2 in high amounts (Kelloff, 1999; Le et al., 2000; Willett, 2001; Yip-Schneider, 2000).

The compounds derived from plant materials having anticancer properties exhibit anti-tumor activities and directing the pathways to tumor cell cycle and cell death (Kunnumakkara et al., 2010; Singh et al., 2002). NF-Kb activation was suppressed by cucurmin (Bisht et al., 2010; Singh and Aggarwal, 1995) and down-regulate the expression of NF-kB–regulated gene produces with roles in proliferation (cyclin-D1, cyclooxygenase-2 (COX-2) and c-myc),anti-apoptosis (X-linked inhibitor of apoptosis protein, Bcl-2, Bcl-xL, and cellular inhibitor of apoptosis protein-1 (cIAP-1)), invasion (matrix metalloproteinase-9 (MMP-9)), metastasis and angiogenesis (VEGF and interleukin-8) (Aggarwal et al., 2006; Mukhopadhyay et al., 2002). Moreover, these phytochemicals encourages the cell death of tumor cells all through the cleavage of the proapoptotic protein BID, activation of caspases and release of cytochrome-C (Anto, 2002; Friedman et al., 2009). In addition to cucurmin, diflourinated-cucurmin (CDF) which is an analogue of cucurmin found in turmeric, has been reported to decrease pancreatic cancer cell survival, clonogenecity, formation of pancreatospheres, invasive cell migration and cancer stem cell (CSC) function in human pancreatic cancer cells. Bioavailability and tissue distribution of curcumin and CDF can be increased through their complexes with cyclodextrin.

Hypoxia-inducible factors (HIFs) and NF-κB are significant to proliferation of cancer cell growth. Both factors are regulated by heat shock protein 90 (Hsp90). In pancreatic cancer cell lines, it also disrupt angiogenesis via modulating HIF-1α and NF-κB, inhibitign COX-2, platelet derived growth factor, VEGF, angiopoietin 1, angiopoietin 2, and TGFβ secretion, suppression of NF-κB, HSP90, and HIF-1α transcription, as well as also enhancing the expression of miR-7 and subsequently lowering expression of SET8, respectively (Ma et al., 2014; Nagaraju et al., 2015; Youns and Fathy, 2013). Curcuminoids induces apoptosis by potentiating natural killer (NK) cell cytotoxic function (Fiala, 2015; Halder et al., 2015). Curcumin plays antitumor effects in MIA PaCa-2 cellsby enhancing apoptosis of MIA PaCa-2 cells of nude mice. It also downregulates the transcription nuclear factor NF-kappa B and NF-kappa B-regulated gene products (Bimonte et al., 2013; Kesharwani et al., 2015).

Curcumin significantly decreased cell proliferation, which was associated with increased expression of the p21/CIP1 and p27/KIP1 cyclin-dependent kinase inhibitors, and inhibited expression of cyclin D1. In addition, curcumin induced apoptosis by decreasing the Bcl-2/Bax protein ratio and increasing caspase-9/3 activation in the pancreatic cancer cells. Using siRNA against FOXO1, and Akt inhibitor and activator, the present study confirmed that curcumin induced the expression of FOXO1 by inhibition of phosphoinositide 3-kinase/Akt signaling, leading to cell cycle arrest and apoptosis. In conclusion, these findings offer support for a mechanism that may underlie the anti-neoplastic effects of curcumin and justify further investigation to examine the potential roles for activators of FOXO1 in the treatment and prevention of pancreatic cancer (Zhao et al., 2015).

Bladder cancer

A crucial health threat of the bladder throughout the word is Transitional cell carcinoma (TCC) (Holmäng, 2000; Saini et al., 2011). The mainstay of therapy for the majority of patients is complete transurethral resection of tumor followed by intravesical instillation of antitumor agents (Herr and Morales, 2008; Morales et al., 2002). The growing interest has been observed in utilizing plant food-derived phytochemicals having ability to lower the occurrence of variety of tumors. The benefit of these food derived chemicals is that these are relatively non-toxic (Jobin et al., 1999; Majid et al., 2011). In prospects, suggested by cucurmin to the cellular biochemical progression regulations includes receptor tyrosine kinase, inhibition of nitric oxide synthase and protein kinase C activities and the modification of nuclear factor p53, jB transcriptional factors cjun/AP-1 (Choudhuri et al., 2002; Kamat et al., 2009b). Curcumin activity inhibits the pathways of cyclooxygenase, lipoxygenase and arachidonic acid metabolism (Shu et al., 2011; Squires et al., 2003). Furthermore, the disposition and bio-activation of chemical carcinogens is modulated by the activities of certain enzymes through cucurmin (Iqbal et al., 2003; Valentini et al.,

2009). It also reduces the rate of colorectal cancer (Chauhan, 2002) and prevalence of urothelial malignancies (Sindhwani et al., 2000) in parts of worlds where cucurmin used as a part of diet. Cucurmin was reported to prompt G2/M arrest of T24 cells (Deng et al., 2008) and apoptosis of MBT-2 cells (Sindhwani and others 2001). Furthermore, in a mouse intravesical tumor implantation model cucurmin efficiently prohibit tumor growth and implantation and in the rodent model carcinogenesis system obiviate OH-BBN-induced bladder carcinogenesis (Zafar et al., 2003).

Krüppel-like factor 5 (KLF5) has significant role in normal and cancer cell proliferation via modulating cell cycle progression. The expression of Hippo pathway effectors such as TAZ and YAP are down regulated with curcumin treatment. In bladder cancer cell lines, curcumin also exhibited the inhibitory effects on tumor growth and the pro-proliferative YAP/TAZ/KLF5/cyclin D1 axis via promoting KLF5 proteasome-dependent degradation through targeting YAP/TAZ (Shakor et al., 2014; Xi et al., 2015).

In bladder human cancer cell lines, curcumin (10 μm) inhibited cell viability, cell invasive activity and the MMP-2/9 activities, respectively. It also enhanced the intracellular ROS concentration and heme oxygenase-1 protein and mRNA expression. The knock down of heme oxygenase-1 by siRNA was accompanied with the anti-invasive activity of curcumin. Moreover, heme oxygenase-1 protein expression was induced by curcumin in the bladder tissue of murine orthotopic bladder tumor model (Watanabe et al., 2011). Curcumin may mediate epigenetic modulation of expression of microRNAs (miRNA). It induces hypomethylation of the miR-203 promoter and subsequent up regulation of miR-203 expression (Saini et al., 2011).

It also prevented from the proliferation of human bladder T24 cells through inhibiting the Aurora A promoter activity and mRNA expression, suppressing phosphorylation of Aurora A and its downstream target histone H3. Curcumin also induced the G(2)/M cell cycle arrest, and reduced the cell division (Liu et al., 2011). The treatment of curcumin to *in vivo* tumors of animals significantly decreased the expression of Cox-2 by 8% and Cyclin D1 by 13% whilst these expressions are regulated by NF-kappaB (Leite et al., 2009). A group of researchers Tharakan et al. (2010) explored the chemopreventive role of curcumin by lowering the proliferation marker Ki-67 and microvessel density (CD31), abolishing the constitutive activation of NF-kappaB in the tumor tissue; inducing apoptosis, and decreasing VEGF, cyclin D1, c-myc, COX-2, and Bcl-2 expression in the bladder cancer tissue. In another study conducted by Chadalapaka et al. (2008), curcumin (10 to 25 micromol/L) exterted preventing mechanism in athymic nude mice bearing KU7 cells against 253JB-V and KU7 bladder cancer cell growth via inducing apoptosis, lowering expression of the proapoptotic protein survivin and the angiogenic proteins VEGF and VEGF receptor 1 (VEGFR1), and also decreased Sp1, Sp3, and Sp4 protein levels. Likewise, work of Tian et al. (2011) investigated that curcumin protect from the human bladder cancer cells through inducting apoptotic cell death, G2/M phase rest, downregulating anti-apoptotic Bcl-2 and Survivin protein, and increasing Bax and p53 expression (Tian et al., 2008). Cigarette smokeare associated with the proliferation of the expression of the NF-kB-,COX-2 and VEGF. Curcumin treatment induced cell cycle arrest, DNA fragmentation and down regulated these expressions in both IFN-alpha-resistant (KU-7) and IFN-alpha-sensitive (RT4V6) bladder cancer cell lines (Kamat et al., 2009a).

Curcumin suppresses the growth of T24 cells via inducing G2/M arrest, down-regulating cyclin A and up-regulating cyclin-dependent kinase (Cdk) inhibitor p21 (WAF1/CIP1), lowering the levels of COX-2 mRNA and protein expression in a concentration-dependent manner, effects associated with the (Li-duan et al., 2006; Parkin et al., 2005). It also show cytotoxic effect on bladder cancer EJ cell via cell phase arrest, inducing apoptosis, down-regulating expressions of NF-kappaB and Cyclin D1 (Sun et al., 2014).

Oral cancer

Recently, an increased prevalence of oral cancer, particularly tongue cancer, was indicated among young adults and this might be associated with the use of smoke-less tobacco (Gandhi et al., 2011). Experimental oral carcinogenesis model was developed by continuous application of a water-soluble carcinogen 4-NQO3 to rats. As reviewed by Gerson (1990), oral lesions in rats caused by 4-NQO are more similar to human lesions as when the 4-NQO is present in the drinking water results in many endophytic and ulcerated tongue lesions (Shklar and Schwartz, 1993).

Cucurmin is suspected to modulate the enzyme activities in the target organ (Chang et al., 2010). Although the effect of Cucurmin on DT-diaphorase activity has not been reported, Shih and Lin (1993) described that dietary exposure of turmeric which contains 1–5% Cucurmin decrease cytochrome b and cytochrome P-450 levels and increased glutathione content and glutathione 5-transferase activity in female Swiss mice liver. It may be likely that the drug-metabolizing system in the tongue will behave in a manner similar to that in the liver, which in turn may influence the tumorigenicity of 4-NQO.

Cucurmin not only lower the expression of MMP-2 and MMP-9 to inhibit invasiveness in oral cancer but also modulates the expression of EMT markers, such as Twist, Snail, and E-cadherin, and induces p53 expression (Lee et al., 2015). Recently, de Paiva Gonçalves et al. (2015) determined that orally curcumin (100 mg/kg) administrated for the 3 months significantly lowered the expression of SOCS1 e -3, Bcl-2, PCNA, and STAT3 during oral carcinogenesis induced by 4-NQO. It also lowered the cellular atypia and diminished the expression of the genes associated with epithelial-mesenchymal transition (EMT). It also inhibits SCC-25 cells invasion, down regulates MMP-2, MMP-9, uPAR and uPA expression, regulates the p-EGFR and EGFR downstream signaling molecules including ERK1/2, Akt, and STAT3, as well as also lowers the EGF-induced phosphorylation of EGFR and suppresses EGF-triggered SCC-25 cells invasion in dose dependent manner (Zhen et al., 2014). Curcumin suppresses the transcription factors AP-1 and NF-kB in the HPV16-positive oral carcinoma cell line 93VU147T (Mishra et al., 2009; Young et al., 2014).

In another study conducted by (Chang et al., 2010), curcumin activated the p38, activated the C/EBP alpha trans-activator by interacting with binding elements in the IGFBP-5

promoter. Curcumin also inhibited the oral carcinogenesis in SAS oral cancer cells through upregulating the upregulation of C/EBPalpha and IGFBP-5 (Chang et al., 2010). Moreover, curcumin prevents from the squamous cell carcinoma (SCC) incidence via significantly decreasing the oral visible tumor incidence and the tumor volume, the numbers of SCC, papillomas, and dysplasic lesions, respectively. Curcumin lowers bromodeoxyuridine (BrdU)-labeling index in hyperplasia, dysplasia, and papillomas as well as increased the apoptotic index suppressed the angiogenesis in papilloma and SCC (Li et al., 2005).

Oesophageal cancer

An innate component of the carcinogenic progression is the resistance to chemo-therapeutic medicines and cancer cell to apoptosis (Parkin et al., 2005). Researchers are more emphasizing on the promising role of phyto-chemicals as a therapeutic mediator against several ailments. Among these phyto-chemicals, cucurmin exhibits momentous chemo-preventive effects against several malignancies (Surh, 2003). Cucurmin induces apoptotic cell death in malignant cells elucidated by various researches and to be both p53 dependent and independent (Salvioli et al., 2007) (Karunagaran et al., 2005; Syng-ai et al., 2004). Increasing evidence is observed that cells resistant to apoptosis died because of cucurmin (Holy, 2002; Wolanin, 2006). Cucurmin encourages defects in micronucleation and cytokinesis, arrest within the G2/M phases of the cell cycle, together with mitotic spindle disruption and dependable to mitotic catastrophe (MC) (a type of cell death) (Magalska et al., 2006; Wolanin, 2006). Recently, curing with cucurmin induce auto-phagic cell deaths in malignant-cells (Aoki et al., 2007; Degterev and Yuan, 2008). It also inhibits different objects such as NF-kB, COX-2 and kinases associated with endurance signaling (NIK, AKT and IKK), cell proliferation and cell cycle regulation (Aggarwal et al., 2003; Castedo et al., 2004). Lately, in cucurmin induced MC, down regulation of the surviving proteins is suspected (Magalska et al., 2006; Wolanin, 2006). Cucurmin induces cell death and it was observed that how chemo-therapeutic mediator are often resistant to cell death in oesophageal tumors, and the molecular characteristics linked with the susceptibility of this agent (Duvoix et al., 2005). Cucurmin mainly induces MC in prone cells. Additionally, autophagy or apoptosis can convoy MC – and in a given cell line it is possibly dependent on the active death signaling pathways (Jana, 2004). Si et al. (2007) illustrated that cucurmin has other molecular effects that could possibly count for both mitotic death mechanism and pleiotropic actions. Cytotoxicity associated with the capacity of cucurmin to accumulate the mitotic regulator cyclin B1 and to raise the levels of poly-ubiquitinated proteins. There is reliable indication that cucurmin can influence multiple targets due to its inhibitory effects on the ubiquitin proteasome system (UPS).

The modulation of P 450 2 E1-dependent AOM metabolism was intervened through cucurmin. It was stated that esophageal cytochrome P 450 isozyme triggered the bioactivation of NMBA (Hodgson et al., 1980). In the initial phase the influence of cucurmin on the metabolizing enzymes are imperative for the blocking effects on NMBA induced esophageal carcinogenesis (Hirose and Ohnishi, 1997). Shih and Lin (1993) have investigated that in mouse fibro-blasts the formation of 8-hydroxydeoxyguanosine and TPA-induced lipid peroxidation were inhibited by cucurmin. On esophageal carcinogenesis, the chemo-preventive effects were shown due to the antioxidant potential. Similarly the formation of adduct benzo (a) 9-pyrene-induced DNA were subdued by cucurmin (Huang et al., 1992). Cucurmin has the potential that in the esophagus it prevents adduct formation by NMBA. The multifarious pharma-cological effects of cucurmin includes the prohibition of the arachidonic acid pathway (lipoxygenase and cyclooxygenase) and in esophageal carcinogenesis it prevent ornithine decarboxylase (ODC) activity (Lu et al., 1993) and inhibition of Notch signaling which is associated with the development of oesophageal cancer.

Bone cancer

Cucurmin exhibited antitumor activity in bone cancer against fibro-sarcoma cells. It inhibited the expression of IL-6 and IL-11 and NF-jB that leads to increased apoptotic activity in fibro-sarcoma cells (Kondo et al., 2001; Kwak, 2006). Cucurmin suppressed MMP-13 expression in chondro-sarcoma cells. Cucurmin inhibited the tumor-induced angiogenesis and protein-1 transcription activator in fibrosarcoma cells via down regulation of expression of genes that are associated with angiogenesis like MMP-9 and VEGF. Additionally, in cells of human osteo-sarcoma cucurmin inhibit the ERK expression and also induce the apoptosis through down-regulating the expression of Bcl-2 in a number of osteosarcoma cells (Periyasamy and Sánchez, 2002). *In vivo* study dietary Cucurmin combined with cisplatin given to rats and its effects were investigated. The results showed that this combination modulate the tumor marker indices of cells of fibro-sarcoma to normal controls. When cucurmin combined with radiotherapy for the sake of treatment of this fibro-sarcoma this results in reduced radio-resistance and enhanced tumor cell-killing in mice having fibro-sarcoma, for instance; it substantially inhibit the radiation-induced NF-jB and ERK expression (Norris et al., 1999).

Curcumin modulates the TGF-β signaling that occurs owing to bone matrix degradation by up regulating the metastasis inhibitory bone morphogenic protein-7 (BMP- 7) (Dorai et al., 2014; Papież, 2012; Webster et al., 2014; Yamaguchi et al., 2014). The administration of curcumin (30 μmol/L) has anticancer effect on human osteosarcoma drug resistant cell line MNNG/HOS/MTX by down-regulating the P-gp expression of MNNG/HOS/MTX cells as well as also suppresses the invasion, proliferation, and metastasis of osteosarcoma MDR cells (Si et al., 2007). Curcumin has exhibited anti-proliferative mechanisms in human osteosarcoma U2OS cells through multiple mechanisms such as inducing DNA fragmentation and apoptotic bodies, elevating the expression of caspase-9 and caspases-3/-7, up-regulating the protein expression levels of cytochrome c, cleaved caspase-3/caspase-9, Apaf-1 and Bad and down regulating the protein expression level of p-Akt, respectively (Webster et al., 2014; Yang, 2013). Treating Lewis lung carcinoma-

(LLC)-bearing female C57BL/6 rats with curcumin curcumin (2% or 4%), it significantly lowered the bone volume/total volume ratio, connectivity density and trabecular number, and enhanced the structure model index and trabecular separation in vertebral bodies. Similar changes such as significant reduction in cortical bone area and thickness, and plasma concentrations of osteocalcin and enhancement in the tartrate-resistant acid phosphate 5b in mice were observed in the femoral bone induced by the curcumin (Yang, 2013). Curcumin modulates the expression of Bcl2, p53-upregulated modulator of apoptosis (PUMA), caspase-activated DNase (CAD) along with increased the manifestation of genes of receptors for M-CSF and GM-CSF in bone marrow cell (BMC) (Fossey et al., 2011; Vishvakarma et al., 2012). Curcumin shows anticancer mechanism

Table 1. Effect of cucurmin on different cancers.

Sr. no.	Cancer type	Mechanism	Reference
1	Colon cancer	Activating apoptosis of adipocytes Inhibiting angiogenesis in adipose tissue	(Ejaz et al., 2009)
2	Cervical cancer	Exhibited antitumor activity in HPV-associated cells Modulates the expression and function of P-gp in multidrug-resistant human KB-V1 cells Down-regulation of viral oncogenes, NF-jB and AP-1	(Devi et al., 2015; Radhakrishnan et al., 2014)
3	Uterine cancer	Down-regulation of Ets-1 Down-regulation of Bcl-2 expression	(Yu and Shah, 2007)
4	Ovarian cancer	Inhibit the activation of NF-jB and allied gene products Suppresses STAT-3	(Chakravarti et al., 2010; Rajasingh et al., 2006)
5	Prostate cancer	Activation of caspase-3 enzyme Inhibition of MMP-9 than MMP-2 Inhibits nitric oxide production and NFkB, Inhibit c-Fos, c-Jun, and AP-1 activity Inhibit protein kinase C, phosphorylase kinase, EGF receptor (EGF-R), erbB2, and ornithine decarboxylase Inhibited the development of azoxymethane-induced colonic Inhibition of activity and expression of the enzyme COX-2	(Mukhopadhyay et al., 2001; Onoda and Inano, 2000)
6	Head and neck cancer	Inhibits the activity of NF-nB downregulates the antiapoptotic proteins bcl-2 and bcl-XL decreased expression of cyclin D1 Prevent InB phosphorylation	(Mukhopadhyay et al., 2002)
7	Breast cancer	Inhibit cytochrome P450 and UDP-glucuronosyl transferases, reduced thioacetamide- and endotoxin Inhibition of the expression of proinflammatory cytokines (tumor necrosis factor-a and IL-1b), transcription factors (NFkB), and enzymes (iNOS) Reduced the indomethacin-Induced intestinal damage	(Ramamoorthi and Sivalingam, 2014)
8	Pulmonary cancer	Inhibit lipopolysaccharide (LPS)-induced production of TNF-a Protective role against the development of BLM-induced pulmonary fibrosis	(Chan et al., 1998; Gescher et al., 1998)
9	Stomach and gastric cancer	Inhibition of inducible nitric oxide synthase (iNOS) Reduced the basal gastric acid secretion Inhibit superoxide radical, hydroxyl radical, and cytotoxic peroxynitrite compound Suppresses the proliferation of Helicobacter pylori Inhibit NF-B activation	(Uchida and Kawakishi, 1990; Zaidi et al., 2009)
10	Pancreatic cancer	Suppress NF-kB activation inhibitor of apoptosis protein-1 (cIAP-1) Inhibit cyclooxygenase-2 Inhibit (COX-2), cyclin D1, and c-myc Induce the apoptosis of tumor cells	(Aggarwal et al., 2006; Anto, 2002)
11	Bladder cancer	Inhibition of arachidonic acid metabolism, Inhibition of lipoxygenase Cycloxygenase activity Curcumin induced apoptosis of MBT-2 cells Induced apoptosis of G2/M arrest of T24 cells Inhibited tumor implantation and growth in a mouse intravesical Inhibits tumor metastasis, Invasion, and angiogenesis	(Kunnumakkara et al., 2007; Sindhwani et al., 2000; Squires et al., 2003; Zafar et al., 2003)
12	Oral cancer	Inhibits 12-O-tetradecanoylphorbol-13-acetate-induced lipid peroxidation and 8-hydroxyguanosine formation in mouse fibroblasts inhibit benzo(a)pyrene-mediated DNA adduci formation Inhibits preneoplastic lesions of colon cancer Decrease cytochrome bs and cytochrome P-450 levels	(Huang et al., 1992; Rao et al., 1993)
13	Oesophageal cancer	Induce autophagic cell death in malignant cells Inhibit NF-kB, COX-2 and kinases (IKK, NIK, and AKT) downregulation of the survivin protein Inhibition of azoxymethane (AOM) Blocking effect on NMBA-Induced esophageal carcinogenesis Inhibition of the arachidonic acid pathway (lipoxygenase and cyclooxygenase) Inhibition of ornithine decarboxylase (ODC) activity	(Aoki et al., 2007; Castedo et al., 2004; Magalska et al., 2006; Wolanin, 2006)
14	Bone cancer	Inhibiting NF-jB & expression of IL-6 and IL-11 Abolishing the inhibitory effect of TGF-b on GR-mediated gene expression in fibrosarcoma cells Suppressed MMP-13 expression Inhibit activator protein-1 Inhibit the ERK expression Down-regulating the Bcl-2 expression	(Anto, 2002; Kondo et al., 2001; Kwak, 2006; Periyasamy and Sánchez, 2002)

against HOS cells by blocking cells in G(2)/M and G(1)/S phases accompanied by down-regulation of cyclin cdc2, D1, and cyclin B1, respectively and activating the caspase-3 pathway (Lee et al., 2009). In Ewing sarcoma cell line SK-NEP-1, curcumin (4 μM) up regulated cleaved caspase 3 down regulated phospho-Akt, suppressing colony formation and inducing apoptosis (Singh and Singh, 2009). It also induces cell cycle G1 arrest, induces apoptosis, upregulates Bak, Bax, and p-Bad, down regulates Bcl-2, significantly lowered mitochondrial membrane potential, enhances the concentrations of mitochondrial cytochrome C and caspase-3 in U2OS cells in a time-and dose-dependent manner (Dhule et al., 2014; Jin et al., 2009).

Skin cancer

Curcumin has inhibitory effects on the multiple myeloma (MM) RPMI 8226 cell line) in a time and dose dependent manner through up regulating the expression of the p53 and Bax genes and down regulating the expression of the MDM2 gene. Curcumin promotes the apoptosis in the MM RPMI 8226 cells by up regulating p53 protein expression (Li et al., 2014). Similarly, Mcl-1 expression is also down-regulated (MM survival factor) by curcumin treatment that induces the cell death (Gomez-Bougie et al., 2014). Similarly, it stimulates the expression of pro-apoptotic Bax, inhibits the activation of anti-apoptotic Bcl-2 and Mcl-1, cleaves Caspase-3 and caspase-8, alters the expressions of proteins NF-κB, p38 and p53, and induced DNA double strand breaks in skin cancer cell lines in dose-dependent manners (Jiang et al., 2014). Recently, different treatments of curcumin (5, 10, 15, 20, 25, 30, 35, 40 and 50 umol/L) for 24, 48 and 72 hours showed inhibitory effect on STAT3 mRNA in A431 cells. It also lowered the invasive ability through suppressing the activation of STAT3 signal pathway and expression of STAT3 (Wu et al., 2015). The administration of curcumin (0.02% wt/wt) in diet fed for 14 week remarkably lowered the 7,12-dimethylbenz(a)anthracene (DMBA)-tetradecanoyl phorbol-13-acetate (TPA) two-stage skin carcinogenesis tumor multiplicity by 53%. It also blocks the cellular propagation in the G2/M stage followed by cellular apoptosis (Faião-Flores et al., 2015; Kim et al., 2014; Sun et al., 2014). Curcumin seems to inhibit skin SCCa growth and blocks tumor development by inhibiting pS6 even when gavage is used to deliver curcumin, indicating even more important effects in future experiments with local application (Phillips et al., 2011).

Conclusion

Cucurmin is a non-toxic, naturally occurring food component having a wide spectrum of biological functions/activities and highly promising natural antioxidant. Cucurmin suppresses proliferation (cyclin D1, cyclooxygenase-2 (COX-2), angiogenesis (interleukin-8 and VEGF), invasion (matrix metalloproteinase-9 (MMP-9), NF-kB activation, and metastasis and it down-regulate the expression of gene products regulated by NF-kB that have roles in anti-apoptosis (cellular inhibitor of apoptosis protein-1 (cIAP-1), Bcl-2, X-linked inhibitor of apoptosis protein and Bcl-xL). Additionally, it also prevents assorted targets for instance; COX-2, NF-kB, and kinases linked with cell proliferation (ERK), survival signaling (IKK, NIK and AKT), and cell cycle regulation.

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