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Chapter 11

Phytochemicals and Cancer – Possible Molecular Targets of Phytochemicals in Cancer Prevention and Therapy

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/59873

1. Introduction

Phytochemicals and their synthetic derivatives have, over the decades, attracted huge attention and made significant contribution in modern drug discovery programs for their relevance in leveraging the severity or cure of several human diseases, including cancer. These natural products and their derivatives thereof have demonstrated immense pharmacological and biological properties. Although the molecular mechanisms of action of a majority of these phytochemicals are yet to be elucidated, cumulative evidence and the continued generation of new scientific data on their health benefits in disease prevention and cure have accrued over the years. Recent advancement in molecular biology, high throughput screening, biomarker identifications, target selection and genomic approaches have enabled researchers to understand salient interactions of natural products or their derivatives with cancer cells.

Most phytochemicals exhibit their pharmacologic effects in nature through a multi-targeted approach; a property that is highly desirable since therapy for carcinomas invariably involves dysregulation of multiple genes and associated cell-signalling pathways at various stages of initiation, progression and metastasis. On the other hand, in cancer initiation and progression, acquired genetic alterations, microenvironment-mediated epigenetic (heritable changes in gene activity and expression that occur without alteration in DNA sequences and are sufficiently powerful to regulate the dynamics of gene expression) perturbations have primarily been considered to play an important role in neoplastic development [9]. Genetic factors which control epigenetic modifications have been extensively documented [53].

One of the most widely studied phytochemical with anticancer properties is curcumin. Indeed, curcumin together with a number of related chemically-defined derivatives have been used

extensively in the treatment of a number of malignant growths, such as breast cancer (Figure 1). The rhizome of the plant *Curcuma longa* L., commonly known as turmeric, has been used for centuries as a spice and colouring agent. The dry rhizome of turmeric contains curcumin, the main bioactive component. Curcumin displays a diverse range of molecular targets, supporting the concept that it acts upon numerous biochemical and molecular cascades (Figure 2). Although the precise mode of action of this compound is yet to be fully elucidated, studies have shown that the chemopreventive action of curcumin might be due to its ability to induce apoptosis by several pathways. Curcumin physically binds to as many as 33 different proteins, including thioredoxin reductase, cyclooxygenase-2, (COX-2), protein kinase C, 5-lipoxygenase (5-LOX), and tubulin. Various molecular targets modulated by this agent include transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation, and apoptosis. Since phytochemicals exhibit their therapeutic effect through multi-mechanism of action, research into the mechanism of action of curcumin in cancer has demonstrated its relevance in various biochemical pathways. The modulation of anti-apoptotic and survival pathways by curcumin as a strategy to induce apoptosis in cancer cells is well documented as well as its ability to inhibit proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell-signalling proteins [29, 48]. A list of some of apoptotic and growth inhibitory pathways activated by curcumin in tumour cells has been well documented [47].

Several reports indicate conflicting evidence on the sensitivity of different cancer cells to the effect of the same phytochemical content of extracts in exhibiting their anti-proliferative effect. This review will therefore focus on recent research developments in anticancer therapy using curcumin, as a representative plant-derived compound, against breast, lung, colorectal, cervical and prostate cancers, generated between 2008 and 2014.

2. Curcumin and breast cancer

Tumour progression is characterised by a mass formed by multiple populations of cells with mechanisms capable of inhibiting apoptosis, while promoting survival pathways and the invasion of healthy tissues through the blood and lymphatic circulation. The manifestation of breast cancer can be determined by the expression of receptors to oestrogen (ER) and to progesterone (PR) and of Her2 (c-erbB2, Her2/neu). Triple-negative breast cancer (TNBC) lacks the expression of the oestrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (HER2/EGFR2) and is an aggressive breast cancer phenotype with a poor prognosis. The p27, a CIP/KIP member, is a cyclin-dependent kinase inhibitor that causes G_1 arrest by inhibiting G_1 cyclin-CDK activities and the reduction of p27 is initiated by enhanced ubiquitin-mediated degradation, in which the Her2/Grb2/MAPK pathway has been implicated in the decrease of p27 stability. The effect of curcumin has been reported to stabilise p27 levels, a lack of which is associated with poor prognosis in breast cancer. In order to investigate whether this effect is mediated through changes in the S-phase kinase-associated protein 2 (Skp2) or Her2 expression, Sun and co-workers determined the inhibitory effect of curcumin on Skp2-mediated p27 ubiquitination in Her2/Skp2-overexpressing cancer cell lines

http://dx.doi.org/10.5772/59873

(MDA-MB-231/Her2 cells) [57]. Their findings revealed that curcumin represses cell proliferation, induces G_1 arrest at a low dosage, and triggers apoptosis at a higher dosage and blocks cell migration in MDA-MB-231/Her2 cells. Curcumin at low dose was also shown to increases p27 and decreases Skp2, Her2, Cyclin E, CDK kinases in a time- and dose-dependent manner, a finding that is suggestive that p27, Skp2 and Her2 may be involved in the curcumin-induced growth inhibition in MDA-MB-231/Her2 cells. On the contrary, higher doses of curcumin produce a dose-dependent apoptotic death in MDA-MB-231/Her2 cells, an event that was observed to be related to cleaved forms of PARP and caspase-3 [57]. [16] on the other hand observed that since the F-box protein S-phase kinase-associated protein 2 (Skp2), which acts as an oncogene through targeting p27 for degradation, is overexpressed in many different human cancers; and that since curcumin induces p27 expression and growth arrest through the inhibition of Skp2 in MDA-MB-231 cells, a therapeutic strategy that could be designed to reduce Skp2 may play a central role in the treatment of ER/HER2 negative breast cancers. In another study, curcumin has been shown to exhibit an inhibitory effect on the proliferation of MDA-MB-231 cells and induced G_2/M arrest in a dose-dependent manner. The study further demonstrated curcumin to increase the protein expression levels of p21 and Bax and decreased the levels of p53 and Bcl-2, a finding that suggests that one molecular mechanism by which curcumin inhibits the proliferation of MDA-MB-231 cells could be either through the up-regulation of p21 expression for apoptosis to occur or through the up-regulation of the Bax-to-Bcl-2 ratio [8].

The effect of curcumin in inducing paraptosis in malignant breast cancer cell lines, including MDA-MB-435S, MDA-MB-231, and Hs578T cells has also been demonstrated. Apoptosis was demonstrated to be promoted by vacuolation that results from swelling and fusion of mitochondria and/or the endoplasmic reticulum (ER) of the cell. The importance of protein synthesis in the process was tested by the use of cycloheximide. Cycloheximide was shown to block curcumin-induced vacuolation and subsequent cell death. AIP-1/Alix protein levels, an inhibitor protein of paraptosis, remained increasingly down-regulated in curcumin-treated malignant breast cancer cells while their overexpression decreased curcumin-induced cell death. ERK2 and JNK activation were shown to be associated with curcumin-induced cell death. It was also shown that mitochondrial superoxide acts as a critical early signal in curcumin-induced paraptosis, whereas proteasomal dysfunction was mainly responsible for the paraptotic changes associated with oestrogen receptor (ER) dilation [69]. Other authours have focused on the testing of the potency of curcumin analogues in comparison with curcumin. In one such study, an *ortho*-hydroxy substituted analogue of curcumin (BDMC-A) was analysed for its cytotoxicity. The analogue inhibited MCF-7 cells at a dose equivalent to that of curcumin. Further analysis of the apoptotic mechanism of the analogue, in comparison with curcumin, demonstrated that the analogue exerted more potent effect on the modulation of selective apoptotic markers of the intrinsic pathway: p53, Bcl-2, Bax, cytochrome c, Apaf-1, caspases-9, -3, PARP and those of the extrinsic pathway: FasL, caspase-8, as compared to curcumin. mRNA expression studies for Bcl-2/Bax also buttressed the efficacy of the analogue. An *in silico* molecular docking study with PI3K revealed that the docking of the analogue was more potent compared to curcumin. Increased apoptotic induction by the analogue was also

demonstrated using different techniques in which characteristic apoptotic features such as nuclear fragmentation and chromatin condensation were exhibited [39].

On the other hand, a major metabolite of curcumin tetrahydrocurcumin (THC) has been investigated for its efficacy and associated mechanism of action in MCF-7 cells. The metabolite was shown to exhibit significant cell growth inhibition by inducing MCF-7 cells to undergo mitochondrial apoptosis and G_2/M arrest, while co-treatment of cells with THC and p38 MAPK inhibitor was observed to effectively reverse the dissipation in mitochondrial membrane potential, and was also shown to block THC-mediated Bax up-regulation, Bcl-2 down-regulation, caspase-3 activation as well as p21 up-regulation. This finding thus highlights the role of p38 MAPK in THC-induced mediated apoptosis and G_2/M arrest, and its relevance, following the biotransformation of curcumin *in vivo* in the treatment of breast cancer [20].

Maspin is a serine protease inhibitor, which suppresses tumour growth and metastasis *in vivo* and tumour cell motility and invasion *in vitro*. In another study, curcumin was shown to up-regulate the expression of miR-15a and miR-16 and down-regulate the expression levels of Bcl-2 in MCF-7 treated cells, while silencing of miR-15a and miR-16 expression by specific inhibitors was shown to restore the expression of Bcl-2 levels. It was concluded from that study that curcumin can reduce the expression of Bcl-2 by up-regulating the expression of miR-15a and miR-16 in MCF-7 cells [44, 66].

Chronic inflammation is considered a major risk factor in the development and metastatic progression of cancers, while obesity on the other hand increases the risk of breast cancer in postmenopausal women. In obese individuals, there are increased levels of growth factors including insulin and insulin-like growth factors (IGFs). High insulin levels lead to an increase in the secretion of oestrogen, by binding to the circulating sex hormone binding globulin (SHBG). Consequently, the increased oestrogen-mediated downstream signalling favours breast cancer development.

Recent reports have shown that curcumin inhibits the expression of the pro-inflammatory cytokines CXCL-1 and CXCL-2, thereby enhancing the diminished formation of breast cancer metastasis [28]. In one study, the authours analysed the correlation between the effects of curcumin on miRNA expression using microarray miRNA expression analyses. Their findings revealed curcumin to modulate the expression of a series of miRNAs, including miR181b, in metastatic breast cancer cells while miR181b was observed to down-modulate CXCL-1 and CXCL-2 through a direct binding to their 3′-UTR [28]. [2] have also demonstrated that reduction of CXCL-1 and CXCL-2 messenger RNA levels is NFκB dependent and requires intact IκBα expression. Furthermore, the silencing of CXCL-1 and CXCL-2 was observed to result in down-regulation of several metastasis-promoting genes among which was the cytokine receptor CXCR4. The ability of curcuminoids to prevent transforming growth factor (TGF-β) induction of parathyroid hormone-related protein (PTHrP) and to reduce osteolytic bone destruction by blockade of Smad signalling in breast cancer cells has also been investigated [63]. To further understand the underlying mechanism, the effects of curcuminoids on breast cancer cell secretion of the bone-resorptive peptide PTHrP and on lytic breast cancer bone metastasis were evaluated in the study. Curcumin was shown to inhibit TGF-β-stimulated PTHrP secretion in MDA-MB-231 human breast cancer cells independent of effects on

http://dx.doi.org/10.5772/59873

cell growth inhibition *in vitro*. The effect on TGF-β signalling, reveal decreases in phospho-Smad2/3 and Ets-1 protein levels with no effect on p-38 MAPK-mediated TGF-β signalling [63].

On the other hand, the mechanism of action of EF24, a novel curcumin analogue, in comparison with curcumin has been evaluated on MDA-MB231 breast cancer cells. EF24 and/or curcumin were shown to inhibit HIF-1α protein levels and, the subsequent inhibition of HIF transcriptional activity. The induction of HIF inhibition was demonstrated to occur in a VHL-dependent but proteasome-independent manner. While curcumin was seen to inhibit HIF-1α gene transcription, EF24 on the other hand exerted its activity by inhibiting HIF-1α post-transcription. EF24 was also shown to induce microtubule stabilisation in cells, although it had no stabilising effect on tubulin polymerisation in an *in vitro* assay using purified bovine brain tubulin, a finding that suggests that EF24-induced cytoskeletal disruption in cells may be related to an upstream signalling event rather than the direct binding of EF24 direct to tubulin [59]. In triple negative breast cancer cells however, curcumin was shown to induce DNA damage in association with phosphorylation, increased expression, and cytoplasmic retention of the BRCA1 protein and was shown to promote apoptosis and prevents anchorage-independent growth and migration of the cells [49].

TNF-related apoptosis inducing ligand (TRAIL) has also shown promising anti-cancer therapeutic activity and natural compound such as curcumin could potentially sensitise resistant cancer cells to TRAIL. Although significant percentage of primary tumours resistant to TRAIL-induced apoptosis remains an obstacle to the extensive use of TRAIL-based monotherapies, the combination of TRAIL with curcumin treatment has been investigated in an effort to induce apoptosis in TRAIL-resistant breast cancer cells. Findings revealed the combination to synergistically induce apoptosis in three TRAIL- resistant breast cancer cells due to the effect of curcumin on the expression and activation of TRAIL-associated cell death proteins to be related to differential effects of curcumin on the expression of Mcl-1 and activities of ERK and Akt. Although curcumin-induced production of reactive oxygen species was not observed to affect total expression of DR5 in this study, it was shown to enhance mobilisation of DR5 to the plasma membrane as well as induce the down-regulation of IAP proteins [43].

Another pathway by which curcumin has been shown to induce apoptosis in various malignant cancer cell lines is the induction of apoptosis through the PI3K/Akt signalling pathway. Protein kinase B (PKB) (Akt) is a member of the family of phosphatidylinositol 3-OH-kinase regulated Ser/Thr kinases. When active, Akt regulates cell survival and proliferation in addition to inhibition of apoptosis. At apoptotic concentration, curcumin has been shown to induce Akt phosphorylation, complemented by an increase in phosphorylation of glycogen synthase kinase 3-β (GSK3β), a pro-growth signalling molecule. In the study, the combination of curcumin with a PI3K inhibitor (LY290042) was shown to exhibit synergistic effect in inducing apoptosis while the inhibitor, on the other hand, was shown to attenuate curcumin-induced Akt phosphorylation and activation of GSK3β [27]. Other mechanisms have shown curcumin-treated MDA-MB-435 human breast cancer cells to accumulate in the G_1 phase of the cell cycle, accompanied by the suppression of the expression of Enhancer of Zeste Homolog 2 (EZH2) gene via the stimulation of three major members of the mitogen-activated protein

kinase (MAPK) pathway: c-Jun NH2-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 kinase [15].

Recently, a new type of non-apoptotic cell death, termed paraptosis has been reported to be induced by insulin-like growth factor-1 receptor, epidermal growth factor, and TAJ/TROY, a member of the tumour necrosis factor (TNF) receptor superfamily. Some authours have demonstrated the ability of curcumin to induce paraptosis in malignant breast cancer cell lines, including MDA-MB-435S, MDA-MB-231, and Hs578T cells, by promoting vacuolation consequent of the swelling and fusion of mitochondria and/or the endoplasmic reticulum (ER). Inhibition of protein synthesis was demonstrated to block curcumin-induced vacuolation and subsequent cell death, a finding that underscores the relevance of protein synthesis in the process of paraptosis. The levels of AIP-1/Alix protein, a known paraptosis inhibitor protein complex, were progressively down-regulated in malignant breast cancer cells exposed to curcumin, and AIP-1/Alix overexpression was shown to attenuate curcumin-induced cell death, while ERK2 and JNK activation were positively associated with curcumin-induced cell death [69].

The different mechanisms through which curcumin inhibits cancer cell functions such as cell growth, survival and motility, continue to be widely explored. In one study, the effect of curcumin on the function of integrin $\alpha 6\beta 4$, a laminin adhesion receptor that plays an important role in the invasion and migration of cancer cells, was assessed. The study revealed curcumin to considerably reduce $\alpha 6\beta 4$-dependent breast cancer cell motility and invasion in a concentration-dependent manner, without affecting apoptosis in MDA-MB-435/ $\beta 4\beta 4$-integrin transfectants and MDA-MB-231 breast cancer cell lines. Curcumin was also shown to selectively reduce the basal phosphorylation of $\beta 4$ integrin (Y1494), which is essential in mediating $\alpha 6\beta 4$-dependent phosphatidylinositol 3-kinase activation and cell motility as well as the blocking of $\alpha 6\beta 4$-dependent Akt activation and expression of the cell motility-promoting factor ENPP2 in MDA-MB-435/$\beta 4$ cell line [24]. The control of matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinases (TIMP) activity in recent years has also come to great significance. Matrix metalloproteinases play an important role in remodelling the extracellular matrix and their activities are regulated by tissue inhibitor of metalloproteinases (TIMPs) family. To investigate the role of curcumin in regulating cell metastasis, the effect of curcumin on metastatic MMPs and anti-metastatic TIMPs genes on MDA breast cancer cells has been assessed and was shown at high concentration to up-regulate TIMP-1, -2, -3 and -4 genes after 48 hours of treatment, accompanied by down-regulation of MMP-2 and MMP-9 gene expression levels in a concentration- and time-dependent manner [13]. This finding highlights the role of curcumin in regulating cell metastasis by inhibition of MMP-2 and MMP-9 and the up-regulation of TIMP-1 and TIMP-4 gene expression in breast cancer cells. In another study, the authours tested the comparative effect of the major component of turmeric (curcumin, demethoxycurcumin, *bis*demethoxycurcumin) in the modulation of MMP-3 activity and its secretion in MDA-MB-231 breast cancer cells. Analysis of MMP-3 expression by casein zymography exhibited high expression in MDA-MB-231 invasive breast carcinoma cells, but not in MCF-7 non-invasive breast cancer cells. In the ELISA assays however, MMP-3 levels were shown to be significantly decreased in all curcuminoid treat-

http://dx.doi.org/10.5772/59873

ments while in using zymography, exposure to non-toxic doses of curcuminoid compounds except curcumin, was shown to reduce MMP-3 levels [3].

Other studies have shown that demethoxycurcumin (DMC) inhibits the adhesion, migration and invasion of MDA-MB-231 human breast cancer cells, by decreasing levels of extracellular matrix (ECM) degradation-associated proteins including matrix metalloproteinase-9 (MMP-9), membrane type-1 matrix metalloproteinase (MT1-MMP), urokinase plasminogen activator (uPA) and uPA receptor (uPAR), while those of uPA inhibitor (PAI-1) have been shown to be up-regulated. Demethoxycurcumin was also shown to reduce the expression of intercellular adhesion molecule-1 (ICAM-1) and chemokine receptor 4, (CXCR4), which is involved in the modulation of the tumour metastasis process. The authours also demonstrated that DMC treatment inhibits DNA binding activity of nuclear factor-kappa B (NF-κB), which is known to mediate the expression of MMPs, uPA, uPAR, ICAM-1, and CXCR4, a finding that is suggestive that the mechanism of DMC mediated anti-invasive activity may involve the modulation of the expression of invasion-associated proteins, possibly by targeting NF-κB in MDA-MB-231 cells [68]. Similarly, the effect of curcumin on NF-κB, cell cycle regulatory proteins and matrix metalloproteinases (MMPs) in two breast cancer cell lines (MDA-MB-231 and BT-483) were evaluated. It was shown that Curcumin exhibited its anti-proliferation effect on MDA-MB-231 and BT-483 cells in a time- and dose-dependent manner, while the expression of cyclin D1 in MDA-MB-231 and the expression of CDK4 in BT-483 were shown to decline. MMP1 mRNA expression in BT-483 and MDA-MB-231 significantly decreased in curcumin treatment group when compared with untreated control group [35]; a finding that further buttresses the notion of the involvement of the regulation of the NF-kB inducing gene by curcumin in breast cancer cell proliferation and invasion. The effect of curcumin (diferuloylmethane) on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced MMP-9 expression, cell invasion and the molecular mechanisms involved in MCF-7 cells invasion has also been reported. Curcumin was shown to inhibit TPA-induced MMP-9 expression and cell invasion through suppressing NF-κB and AP-1 activation. It was also revealed to repress TPA-induced phosphorylation of p38 and JNK, and inhibits TPA-induced translocation of PKCα from the cytosol to the membrane, suggesting that curcumin-mediated inhibition of TPA-induced matrix metalloproteinase (MMP)-9 expression and cell invasion is associated with the suppression of the PKCα, MAPK and NF-κB/AP-1 pathway in MCF-7 cells [26]. In another study to evaluate the effects of curcumin on matrixmetalloproteinase-9 (MMP-9) and invasion ability induced by transforming growth factor-β1 (TGF-β1) in MDA-MB-231 cells, it was shown that low doses of curcumin had no obvious toxicity on cells while a change in concentration resulted in a concentration-dependent reduction in cell invasion provoked by TGF-β1. Curcumin was also shown to markedly inhibit TGF-β1-regulated MMP-9 and activation of Smad2, ERK1/2 and p38 in a dose- and time-dependent manner, a mechanism that maybe associated with TGF-β/Smad and TGF-β/ERK signalling [38].

The effect of low concentrations of curcumin has also been tested on patient-derived primary breast cancer-associated fibroblasts (CAF) cells. Cancer-associated fibroblasts actively participate in tumour growth, invasion, and metastasis. This involves many chemokines, growth factors, and matrix metalloproteinases (MMPs), which transmit the message in both directions,

thus allowing cooperative crosstalk between cancer cells and their stroma. Recent reports show that curcumin treatment up-regulates p16INK4A and other tumour suppressor proteins and inactivates the JAK2/STAT3 pathway which results in the reduction level of alpha-smooth muscle actin (α-SMA) and the migration/invasion abilities of CAF cells. Curcumin was also demonstrated to further suppress the expression/secretion of stromal cell-derived factor-1 (SDF-1), interleukin-6 (IL-6), matrix metalloproteinase-2 (MMP-2), MMP-9, and transforming growth factor-β, thereby impeding their paracrine procarcinogenic potential. Intriguingly, these effects were sustained even after curcumin withdrawal and cell splitting. Curcumin-related senescence in this study was shown to be p16INK4A-dependent and occurred with no associated inflammatory secretory phenotype and that curcumin can trigger DNA damage-independent and safe senescence in stromal fibroblasts [14].

The efficacy of curcumin in blocking *Recepteur d'Origine Nantais* (RON) tyrosine kinase–mediated invasion of breast cancer cells has also been analysed. Curcumin-mediated inhibition of RON expression has been shown to result in the blockade of RON ligand, MSP-induced invasion of breast cancer cells and reduced RON expression by distorting p65 protein expression and transcriptional activity. The treatment of MDA-MB-231 cells with pyrrolidine dithiocarbamate, an inhibitor of p65, or small interfering RNA knockdown of p65, leads to the blockage of RON gene expression and MSP-mediated invasion of MDA-MB-231 cells which further highlights the role of curcumin in blocking RON tyrosine kinase-mediated invasion of carcinoma cells [42]. Other studies have focused on the role of curcumin in preventing or delaying the progression of cancer by disruption of epithelial-mesenchymal transition (EMT), a key event in cancer cell invasion and metastasis. The authours showed that curcumin inhibits LPS-induced morphological changes, decreased the expression of LPS-induced markers of EMT such as vimentin, and increased the expression of E-cadherin and as a consequence, the inhibition of motility and invasiveness of MCF-7 and MDA-MB-231 breast cancer cell lines *in vitro*, mediated through the inactivation of NF-κB-Snail signalling pathways [17].

Of equal importance is the frequent association of obesity with breast cancer, an association that is possibly mediated by adipokines. Visfatin, an adipokine, has recently been shown to be related to the development and progression of breast cancer. Hence the consideration that its down-regulation may be a novel strategy for breast cancer therapy has been explored. To investigate this, the effect of curcumin on visfatin gene expression and the characterisation of its functional role in breast cancer have been assessed. It was found that the mRNA and protein levels of visfatin were down-regulated by curcumin in MDA-MB-231, MDA-MB-468, and MCF-7 breast cancer cells, along with decreased activity of constitutive NF-κB which highlights the effect of curcumin to down-regulate visfatin gene expression in human breast cancer cells by a mechanism that is, at least in part, NF-κB dependent [26]. On the other hand obesity has also been shown to results in change in the expression profiles of several adipokines and cytokines including leptin, adiponectin, IL-6, TNF-α and IL-1β. Increased levels of leptin and decreased adiponectin secretions are directly associated with breast cancer development while increased levels of pro-inflammatory cytokines within the tumour microenvironment promote tumour development. The cumulative evidence of different adipokine- and cytokine-mediated

http://dx.doi.org/10.5772/59873

molecular signalling pathways involved in obesity-associated breast cancer have been documented [22].

Furthermore, the development and progression of malignant tumours depends on the formation of new blood vessels inside the tumour through a process termed angiogenesis. It is a vital process that ensues during cancer progression, and depends on the expression and activation of various angiogenic molecules, cytokines, growth factors, kinases and transcription factors. It had been previously demonstrated that the chemokine-like ECM-associated protein osteopontin (OPN) ignites the angiogenic switch by up-regulating the expression of vascular endothelial growth factor (VEGF) in a human breast cancer model. In this study [4], the authours demonstrated that curcumin (diferuloylmethane) abolishes OPN-induced VEGF expression and controls OPN-induced VEGF-dependent breast tumour angiogenesis *in vivo*. It was also observed that curcumin, in combination with anti-VEGF or anti-neuropilin (NRP)-1 antibody, was able to boost anti-angiogenic activity when compared to curcumin alone.

Furthermore, the over-expression of Flap endonuclease 1 (Fen1), a DNA repair-specific nuclease, has been implicated in the development of breast cancer. Nrf-2 is a leading regulator of cellular antioxidant defence systems and its inhibition of proliferation of breast cancer cells through its-mediated down-regulation of Fen1 expression by curcumin has been reported. Curcumin has been demonstrated to inhibit Fen1-dependent proliferation of MCF-7 cells, significantly induce Nrf-2 protein expression and inhibit Fen1 protein expression. It has also been shown to down-regulate Fen1 gene expression in an Nrf-2-dependent manner, as well as causing Nrf-2 translocation from the cytoplasm to the nucleus and to decrease Fen1 promoter activity by decreasing the recruitment of Nrf-2 to the Fen1 promoter [5]. While the abnormal activation of the Wnt/β-catenin signalling pathway and subsequent up-regulation of β-catenin driven downstream targets c-Myc and cyclin D1 is said to be associated with development of breast cancer in another study, the possibility that the efficacy of curcumin in the inhibition of cell proliferation and induction of apoptosis occur through modulation of β-catenin pathway in human breast cancer cells have also been suggested [45].

In order to help circumvent the problem associated with the low bioavailability of curcumin, the activities of analogues of curcumin have been tested in comparison with curcumin. In one study, an analogue of curcumin, GO-Y030, was tested for its efficacy in human breast MDA-MB-231 cell line. Both compounds were shown to reduce cell viability and induce apoptosis, although GO-Y030 was substantially more potent. It was also demonstrated that GO-Y030 was capable of interfering with STAT3 by inhibiting its phosphorylation and transcriptional activity, whereas comparable dosages of curcumin had little or no effect [18]. STAT3 is a persistently activated transcription factor in many cancer types. With regard to STAT3 phosphorylation, another curcumin analogue, FLLL12 was found to be a more potent inhibitor than the other, FLLL11. The reduction of phosphorylation of STAT3 was observed to correlate with the induction of apoptosis (determined by cleavage of PARP and caspase-3) [32]. Similarly, another synthetic curcumin analogue (hydrazinocurcumin) was shown to be more effective than curcumin in inhibiting STAT3 phosphorylation and down-regulation of an array of STAT3 downstream targets which contribute to suppression of cell proliferation, loss of colony formation, depression of cell migration and invasion as well as induction of cell

apoptosis [61]. Inhibition of IkB kinase-nuclear factor-kB signalling pathway by 3,5-*bis*(2-flurobenzylidene)piperidin-4-one (EF24), a novel monoketone analogue of curcumin has also been demonstrated. EF24 has been shown to potently suppress the NF-κB signalling pathway through direct action on IκB kinase (IKK) [21].

Hypoxia-inducible factors (HIFs) are transcription factors that play a central role in the adaptation and response to low oxygen levels in metazoan cells. Curcumin has been attributed with tumour growth inhibiting effects, possibly mediated by promoting hypoxia-inducible factor (HIF) degradation and also as exhibiting properties of an iron chelator, suggesting its potential of inhibiting HIF-α prolyl hydroxylase (PHD) activity. In order to clarify the divergent action of curcumin, researchers studied the concentration- and time-dependent effects of curcumin on HIF-α and -β protein levels and activity in hepatoma and breast carcinoma cell cultures under normoxic and hypoxic conditions. HIF-1α was shown to accumulate in normoxia after the application of higher doses of curcumin. The effect of curcumin was shown to lower HIF-1α and HIF-2α protein levels in hypoxia. HIF-1β (ARNT; arylhydrocarbon nuclear translocator) protein levels and HIF transcriptional activity were also reduced in normoxia and hypoxia after 4 h and 24 h of exposure. Furthermore, curcumin treatment was shown to negatively impact on clonogenic cell survival of Hep3B hepatoma and MCF-7 breast carcinoma cells. Effects of curcumin on cell growth and survival factor expression was suggested to be of potential benefit in the treatment of cancer without a direct radiosensitising influence of the drug on these cells [56].

The effects of curcumin on triple-negative breast cancer (TNBC) cells and the possible molecular mechanisms have been evaluated in MDA-MB-231 cells [57]. The authours examined the anti-proliferative effect of curcumin, its ability to induce apoptosis and the expression levels of extracellular regulated protein kinase (ERK1/2), pERK1/2, EGFR and pEGFR and concluded that the inhibition of the epidermal growth factor receptor (EGFR) signalling pathway is the likely underlying molecular mechanism of curcumin action in these cells. Since the functional interaction between integrin α6β4 and growth factor receptors has been implicated in key signalling pathways important for cancer cell function, the functional interaction between α6β4 and the epidermal growth factor receptor (EGFR) has also been examined. Findings revealed that curcumin is able to disrupt the functional and physical interactions between α6β4 and EGFR, as well as block α6β4/EGFR-dependent functions of carcinoma cells expressing the signalling competent form of α6β4. It has also been established that curcumin inhibits EGF-dependent mobilisation of α6β4 from hemi-desmosomes to the leading edges of migrating cells such as lammelipodia and filopodia, and thereby preventing α6β4 distribution to lipid rafts where functional interactions between α6β4 and EGFR occur. This finding highlights a novel paradigm in which curcumin inhibits α6β4 signalling and functions by altering intracellular localisation of α6β4, preventing its association with signalling receptors such as EGFR [55].

http://dx.doi.org/10.5772/59873

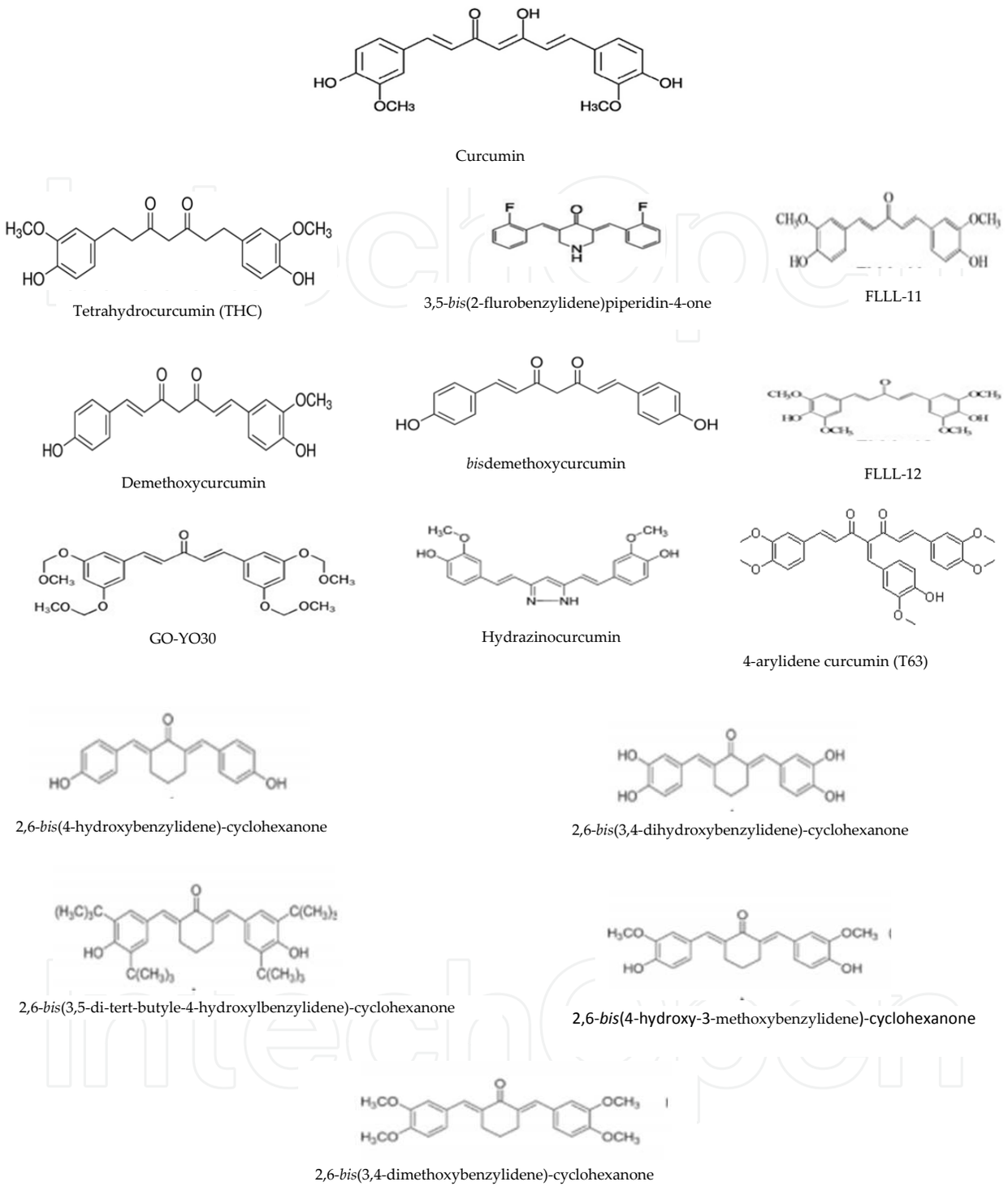

Figure 1. Chemical structure of curcumin and related derivatives/analogues widely used in the treatment of various forms of cancers.

The use of curcumin as potential candidate in the treatment for HER-2-overexpressed breast cancer has also been reported [30]. HER-2 is an important oncoprotein that is overexpressed in about 15–25% of breast cancers. In one particular study, cell growth, cell cycle change, the

anti-mobility effect, signal transduction, and xenograft volume analysis between groups treated with herceptin and/or curcumin were examined. Curcumin was shown to effect a decrease in cell growth of MCF-7, MDA-MB-231, MCF-10A, BT-474, and SK-BR-3-hr breast cancer cell lines while phosphorylation of Akt, MAPK, and expression of NF-κB were shown to be reduced in BT-474 cells, but not in SK-BR-3-hr cells, after treatment with herceptin. Following treatment with curcumin, the HER-2 oncoprotein, phosphorylation of Akt, MAPK and expression of NF-κB were shown to decrease in both BT-474 and SK-BR-3-hr cells [30]. Evidence indicates that curcumin reverses chemo-resistance and sensitises cancer cells to chemotherapy and targeted therapy in breast cancer. Studies have therefore been undertaken to explore curcumin's potential anti-proliferation effects and resistance reversal in anti-oestrogen-resistant breast cancer cell line MCF-7/LCC2 and MCF-7/LCC9. The effect of curcumin treatment revealed anti-proliferative and pro-apoptotic activities and induction of cell cycle arrest at G_2/M interphase. Moreover, the combination of curcumin and tamoxifen exhibited a synergistic survival inhibition in MCF-7/LCC2 and MCF-7/LCC9 cells. It was also revealed that curcumin targets multiple signals that are involved in growth maintenance and resistance acquisition in endocrine resistant cells. In the cell types used, curcumin was shown to suppress the expression of pro-growth and anti-apoptosis molecules, induce inactivation of NF-κB, Src and Akt/mTOR pathways and down-regulates the key epigenetic modifier EZH2 [19]. The chemosensitisation of breast cancer cell by curcumin to 5-fluorouracil (5-FU) has also been demonstrated. 5-Fluorouracil is an antimetabolite which achieves its therapeutic efficacy through inhibition of the enzyme thymidylate synthase (TS), essential for the synthesis and repair of DNA. Prolonged exposure to 5-FU induces TS overexpression, which leads to 5-FU resistance in cancer cells. Curcumin was demonstrated to sensitise the breast cancer cells to 5-FU through TS-dependent down-regulation of NF-κB. Silencing of TS was shown to suppress 5-FU-induced NF-κB activation, whereas inactivation of NF-κB was not shown to affect 5-FU-induced TS up-regulation, a finding that indicates that TS is upstream of NF-κB and is responsible for the regulation of the activation of NF-κB in 5-FU-induced signalling pathway. Although Akt/PI3 kinase and mitogen-activated protein kinase pathways were activated by 5-FU and down-regulated by curcumin, they were not shown to play a role in regulating the synergism in the study [60].

3. Curcumin and lung cancer

The molecular antitumour mechanism of a new 4-arylidene curcumin analogue (T63) has recently been reported to significantly inhibit the proliferation of A549 and H460 human lung cell lines via induction of G_0/G_1 cell cycle arrest and apoptosis. The study implicated reactive oxygen species (ROS)-activated FOXO3a cascade to be responsible to playing a central role in T63-induced cell proliferation inhibition. Enhancement of ROS production by T63 was shown to induce FOXO3a expression and nuclear translocation through activation of p38MAPK and inhibition of AKT, with subsequent elevation of the expression of FOXO3a target genes, including p21, p27, and Bim, as well as increasing the levels of activated caspase-3 and decreased levels of cyclin D1. N-acetylcysteine, an antioxidant, was shown to noticeably block

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the above effects, while small interfering RNA-mediated knockdown of FOXO3a significantly decreased T63-induced cell cycle arrest and apoptosis [34]. Evident in another study, was the ability of curcumin to cause DNA damage and endoplasmic reticulum (ER) stress and mitochondrial-dependent-induced apoptosis through the activation of caspase-3 at a treatment concentration of 30 μM in human lung cancer A549 cells. In contrast, lower concentrations of 5–10 μM curcumin showed no significant apoptotic inducing effect but rather induced G_2/M-phase arrest in A549 cells. It was also shown to increase intracellular oxidative stress, indicators of ER stress, Ca^{2+} levels and the mitochondrial membrane potential in A549 cells thereby highlighting the role of curcumin in the activation of pathways involved in inducing G_2/M-phase arrest and apoptosis [33].

In another effort to finding novel putative intervention sites as chemo-protective and chemotherapeutic target for curcumin in squamous cell lung carcinoma, Sen and co-authours, demonstrated that curcumin induces apoptosis in these cells, while microarray analysis revealed about 34 and 31 genes to be up- and down-regulated, respectively, following curcumin treatment. Likewise, growth arrest and DNA damage genes, GADD45a and peroxiredoxin-I was also shown to be up-regulated more than 2-folds (Sen *et al.,* 2008).

The effect of curcumin in non-small cell lung cancer (NSCLC), the leading cause of cancer-related mortality, has also been evaluated. High expression of Rad51, a key protein in the homologous recombination (HR) pathway of DNA double-strand break repair, plays a key role in chemo- or radio-resistant carcinomas and thus HR represents a novel target for cancer therapy. Studies to evaluate the effect of curcumin in enhancing the effect of mitomycin C (MMC), a DNA inter-strand cross-linking agent, to induce cytotoxicity by decreasing Rad51 expression have been reported. Findings revealed curcumin treatment of non-small lung cancer (NSCLC) cell lines (A549 and H1975) was capable of suppressing MMC-induced MKK1/2–ERK1/2 signal activation and Rad51 protein expression. On the other hand, enhancement of ERK1/2 activation by constitutively active MKK1/2 (MKK1/2-CA) was shown to increase Rad51 protein levels in curcumin and MMC co-treated human lung cells. The synergistic cytotoxic effect induced by curcumin–MMC treatment was established to be decreased by MKK1-CA-mediated enhancement of ERK1/2 activation by a significant degree. On the contrary, the MKK1/2 inhibitor, U0126 was shown to augment the cytotoxicity of curcumin and MMC through down-regulation of ERK1/2 activation and Rad51 expression, while depletion of endogenous Rad51 expression by siRad51 RNA transfection was demonstrated to significantly enhance MMC and/or curcumin-induced cell death and cell growth inhibition. In contrast, an overexpression of Rad51 protected the lung cancer cells from synergistic cytotoxic effects induced by curcumin and MMC. It was thus concluded that Rad51 inhibition may be an additional mechanism of action for enhancing the chemosensitisation of MMC by curcumin in NSCLC [27].

In a similar study, the effect of curcumin treatment on the expression of nuclear factor κB-related proteins *in vitro* and *in vivo* and on growth and metastasis in an intra-lung tumour mouse model alone or in combination with gemcitabine or cisplatin has been assessed. Western blot analyses showed that the expressions of IkB, nuclear p65, cyclooxygenase-2 (COX-2) and p-ERK1/2 were down-regulated by curcumin *in vitro*. In *in vivo*, curcumin was shown to

potentiate gemcitabine- or cisplatin-mediated antitumour effects and was also capable of reducing COX-2 expression in subcutaneous tumours with a decrease in weight of intra-lung tumours accompanied by a significant survival rate increase. The effect of curcumin in the inhibition of COX-2, p65 expression and ERK1/2 activity in NSCLC cells was observed to be associated with decreased survival and increased induction of apoptosis [32].

The anti-metastasis effects and mechanism of curcumin action in lung cancer have also been elucidated. Rac1 is an important small Rho GTPases family protein and has been widely implicated in cytoskeleton rearrangements and cancer cell migration, invasion and metastasis. In order to investigate its role, [5] examined the influence of curcumin on *in vitro* invasiveness of human lung cancer cells and the expression pattern of Rac1. Their findings revealed that curcumin at 10 μM was capable of slightly reducing the proliferation of 801D lung cancer cells with a pronounced inhibitory effect on epidermal growth factor or transforming growth factor β1-induced lung cancer cell migration and invasion. The suppression of invasiveness correlated with the inhibition of Rac1/PAK1 signalling pathways and matrix metalloproteinases (MMP) -2 and -9 protein expression when curcumin treatment was combined with the methods of Rac1 gene silencing and overexpression in lung cancer cells. It was also revealed by laser confocal microscopic analysis that Rac1-regulated actin cytoskeleton rearrangement may be involved in anti-invasion effect of curcumin on lung cancer cell. The authours concluded that low-toxic levels of curcumin could efficiently inhibit migration and invasion of lung cancer cells through inhibition of Rac1/PAK1 signalling pathway and MMP-2 and MMP-9 expression [5].

The effect of curcumin as a chemosensitiser in lung cancer has also been examined on HIF-1α in cisplatin (DDP) sensitive A549 and resistant A549/DDP cell lines. Findings revealed HIF-1α in A549/DDP cells to be overexpressed at both mRNA and protein levels together with a poor response to DDP. It was also shown that HIF-1α abnormality contributes to DDP resistance in A549/DDP lung cancer cells while combined curcumin and DDP treatment was observed to markedly inhibited A549/DDP cells proliferation, reversed DDP resistance and triggered apoptotic death by promoting HIF-1α degradation and activation of caspase-3, respectively. The expression of HIF-1α-dependent P-gp was also observed to decrease in response to curcumin in a dose-dependent manner; a finding that highlights the drug resistant reversing effect of curcumin in lung cancer cells by inhibiting HIF-1α expression and activation of caspase-3 [67].

A novel inflammation-related mechanism for curcumin-induced inhibition of lung tumour growth has also been reported. Neutrophil elastase, an important regulator of inflammatory processes has been found to directly triggered tumour cell proliferation in human lung adenocarcinoma A549 cells. Alpha1-antitrypsin synthesised by tumour cells is a natural inhibitor of neutrophil elastase and curcumin has been shown to counter the decrease of α1-antitrypsin induced by neutrophil elastase by prompting the promoter activity of α1-antitrypsin, thereby promoting its expression in A549 cells. The inhibition of neutrophil elastase-induced proliferation was shown to be dependent on the PI3K/Akt pathway. Knockdown of α1-antitrypsin by siRNA was demonstrated to further enhance the tumour cell proliferation induced by neutrophil elastase and significantly blocked the anti-proliferative effect of curcumin against neutrophil elastase. In *in vivo*, curcumin was also observed to remarkably

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inhibit the primary tumour growth of Lewis lung carcinoma (LLC) in C57BL/6 mice. The authours also demonstrated that curcumin up-regulates the level of α1-antitrypsin in primary tumour tissue by promoting its local expression, while the protein level of neutrophil elastase in tumour tissue was observed to decrease in mice treated with curcumin. This finding further highlights the roles of neutrophil elastase and α1-antitrypsin in modulating lung tumour proliferation in inflammatory microenvironment and the effect of curcumin in inhibiting neutrophil elastase-induced tumour proliferation via the up-regulation of α1-antitrypsin expression *in vitro* and *in vivo* [64].

4. Curcumin and colorectal cancer

Insulin resistance and obesity are associated with increased colorectal cancer (CRC) risk and high reoccurrence rates. The effect of dietary compounds in reducing insulin-induced cell proliferation in normal and metastatic colon epithelial cells has been demonstrated. Murine colon epithelial cells (YAMC) and adenocarcinoma cells (MC38) were treated with docosahexaenoic acid (DHA) or curcumin alone, followed by the combination of co-treatments of the diet-derived compound and insulin. Insulin-stimulated MAPK and MEK phosphorylation was shown to be inhibited by DHA and curcumin in MC38 cancer cells, suggesting that curcumin and DHA are capable of blocking insulin-induced colon cancer cell proliferation *in vitro* via a MEK-mediated mechanism [12]. Other indicators implicate non-steroidal anti-inflammatory drugs (NSAIDs), particularly the highly selective COX-2 inhibitors in the prevention of colon cancer. As such, some authours have demonstrated the effects of diclofenac, a preferential COX-2 inhibitor, and curcumin in inducing apoptosis in colon cancer cells. Both diclofenac and curcumin were shown to lower COX-2 activity and PGE-2 levels while the expression of IκBα was shown to be higher, with a lowered IKK activity suggesting that these agents may suppress the transfer of NF-κB to the nucleus and its pro-inflammatory gene transcription. Both drugs were also shown to down-regulate the level of pro-inflammatory cytokines, TNF-α, IL-1β and IL-2, through the inhibition of NF-κB and subsequent induction of apoptosis, thus confirming the regulatory role of NF-κB in the process [46]. Similarly, targeting nutraceuticals to tumours can enhance their effectiveness. Nanoparticles encapsulating curcumin have been shown to be more effective than the free curcumin, eventually inhibiting NF-κB regulated transcription and angiogenesis [41].

In a study, [50] exposed human colorectal cancer cells to clinically relevant doses of gamma rays, in an attempt to elucidate the mechanism of their radio-resistance. The authours characterised NF-κB activation as a mechanism of inducible radio-resistance in colorectal cancer. Curcumin was shown to inhibit the proliferation and the post-irradiation clonogenic survival of multiple colorectal cancer cell lines. Radiation was observed to stimulate NF-κB activity in a dose- and time-dependent manner, whereas curcumin was shown to suppress this radiation-induced NF-κB activation via inhibition of radiation-induced phosphorylation and degradation of inhibitor of κB alpha, inhibition of κB kinase activity, and the inhibition of Akt phosphorylation. Curcumin was also shown to suppress NF-κB–regulated gene products (Bcl-2, Bcl-xL, inhibitor of apoptosis protein-2, COX-2, and cyclin D1). The authours concluded

that transient inducible NF-κB activation provides a pro-survival response to radiation that may account for development of radio-resistance and that curcumin blocks this signalling pathway and further potentiates the antitumour effects of radiation therapy.

The induction of cellular senescence of human colon cancer cells HCT116 upon curcumin treatment, demonstrating a functional link between senescence and autophagy in curcumin-treated cells, has been reported. Activation of SA-β-galactosidase activity following curcumin treatment has been observed in p53+/+ and p53−/− cells, although the later was less sensitive to the pro-senescent activity. The authours also demonstrated the up-regulation of p53 and p21 proteins in p53+/+ HCT116 cells, while p53-independent induction of p21 was observed in p53−/− HCT116 cell. Senescence of HCT116 cells was shown to be accompanied by autophagy that was confirmed by electron microscopy observations of autophagosomes in the curcumin-treated cells as well as LC3-II expression, puncture staining of LC3 and increased content of acidic vacuoles. Inhibition of autophagy, due to the diminished expression of ATG5 by RNAi, was observed to decrease the number of senescent cells induced by curcumin, but was not shown to lead to increased cell death [40].

5. Curcumin and cervical cancer

Human papillomavirus (HPV) infections remain a leading cause of mortality worldwide and cervical cancer is associated with infection with high risk human papillomaviruses (HPVs). Cervical cancer is the second leading cause of cancer death for women in the world. The effect of low concentration of curcumin on human cervical cancer cell line (HeLa) has been shown to mediate decrease in the cell number and viability, and increase in apoptotic events and superoxide level. Treatment of cells with curcumin was revealed to be toxic even at concentrations as low as 1 μM even though no genotoxic effect was observed in these cells. Since argyrophilic nucleolar protein (AgNOR protein) expression is elevated in malignant cells compared to normal cells, the effect of curcumin-associated changes in size (area) and number of silver deposits were also evaluated. Curcumin was shown to induce decreased AgNOR protein pools, mediated possibly by global DNA hypermethylation observed after low concentration of curcumin treatment [31].

Curcumin is an anti-inflammatory agent that is known to have anti-COX-2 activity. One way of preventing and treating cervical cancer is by targeting COX-2. In order to evaluate the effect of curcumin in cervical cancer, the expression of COX-2 and its precursors have been examined by immunohistochemistry. The inhibitory effect of curcumin on cervical cancer cells was determined via 2-dimensional gel electrophoresis, data analysis, and ingenuity pathway analysis. The authours observed no significant differences in the expression of COX-2 in squamous cell carcinoma, and carcinoma *in situ*, although that was not the case in the expression of COX-2 in adenocarcinoma in comparison to normal and squamous cell carcinoma tissues. However, proteins associated with cancer and the cell cycle were shown to be significantly altered in cultured cells [37].

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Since cervical cancer is associated with infection with high risk human papillomaviruses (HPVs), the molecular mechanism of curcumin induced apoptosis in HPV-positive cervical cancer HeLa, SiHa and CaSki cells have also been evaluated. Curcumin was shown to cause distinct inhibition of human telomerase reverse transcriptase (hTERT), the catalytic core of telomerase thereby reducing proliferation of cancer cells. Findings in the study revealed that curcumin-mediated apoptosis in these cells may be associated with the up-regulation of pro-apoptotic Bax, AIF, release of cytochrome c and down regulation of anti-apoptotic Bcl-2 and Bcl-xL, accompanied by an increase in caspase-3 and -9 activities. As such, the effect of curcumin as an anti-inflammatory and anti-proliferative agent in these cells was shown to be associated with down regulation of COX-2, iNOS and cyclin D1 at varying extents [54]. Recently, in an attempt to develop a curcumin–based therapy for cervical cancer, the effect of curcumin on four human papillomavirus HPV (+) cervical cancer cell lines and normal fibroblasts has been assessed. Curcumin treatment was shown to selectively eliminate a variety of HPV (+) cervical cancers cells (HeLa, ME-180, SiHa, and SW756), suppress the transforming antigen E6, dramatically inhibits the expression of the pro-cancer protein epidermal growth factor receptor (EGFR), and concomitantly induced p53 levels. In addition, vacurin, a colloidal solution of curcumin which is incorporated in clinically used amphipathic vaginal cream was shown to eliminate apposed HeLa cells while suppressing the expression of EGFR [11].

6. Curcumin and prostate cancer

Emerging evidence suggests that chronic inflammation is a major risk factor for the development and metastatic progression of prostate cancer. In evaluating the effect of curcumin on prostate carcinoma growth, apoptosis and metastasis, curcumin was shown to inhibit the translocation of NFκB to the nucleus through the inhibition of the IκB-kinase (IKKβ), leading to stabilisation of the inhibitor of NFκB, IκBα, in PC-3 prostate carcinoma cells. Inhibition of NFκB activity was demonstrated to reduce expression of CXCL-1 and -2 and abolished the autocrine/paracrine loop that links the two chemokines to NFκB. When used in combination with the synthetic IKKβ inhibitor, SC-541, no additive or synergistic effect was observed while treatment of cells with curcumin and siRNA-based knockdown of CXCL-1 and -2 was shown to induce apoptosis, inhibit proliferation and down-regulate several important metastasis-promoting factors like COX-2, SPARC and EFEMP. In an orthotopic mouse model of hematogenous metastasis, treatment with curcumin inhibited statistically significant formation of lung metastasis. The authours concluded that chronic inflammation can induce a metastasis prone phenotype in prostate cancer cells by maintaining a positive pro-inflammatory and pro-metastatic feedback loop between NFκB and CXCL-1/-2, while reduced metastasis formation *in vivo* can be achieved by the disruption of this feedback loop by curcumin-induced inhibition of the NFκB signalling [23].

On the other hand, protein kinase D1 (PKD1), a multifunctional kinase that is highly expressed in normal prostate and decreased expression levels, has been associated with the progression of prostate cancer. Curcumin has been found to activate PKD1, with subsequent changes in β-catenin signalling by hindering nuclear β-catenin transcription activity and increasing the

levels of membrane β-catenin in prostate cancer cells. Modulation of these cellular events by curcumin is shown to correlate with decreased cell proliferation, colony formation, cell motility and enhanced cell-cell aggregation in prostate cancer cells. It has also been demonstrated that inhibition of cell motility is mediated by decreasing the levels of active cofilin, a downstream target of PKD1. The potent anti-cancer effect of curcumin *in vitro* in the study was shown to correlate well with those in prostate cancer xenograft mouse model, thus highlighting a novel molecular mechanism of curcumin action via the activation of PKD1 in prostate cancer cells [58]. The effect of curcumin in suppressing prostate cancer cell invasion, tumour growth, and metastasis has also been assessed. Curcumin was shown to be capable of suppressing epidermal growth factor (EGF)-stimulated and heregulin-stimulated PC-3 cell invasion, as well as androgen-induced LNCaP cell invasion. Treatment of cells with curcumin was also shown to significantly result in reduced matrix metalloproteinase 9 activities and down-regulation of cellular matriptase, a membrane-anchored serine protease with oncogenic roles in tumour formation and invasion. It was also demonstrated that curcumin inhibits the induction effects of androgens and EGF on matriptase activation, as well as the reduction of the activated levels of matriptase after its overexpression. The reduction of activated matriptase in cells by curcumin was also observed to be partly due to its effect on promoting the shedding of matriptase into an extracellular environment without altering matriptase gene expression. In addition, curcumin was also shown to significantly suppress the invasive ability of prostate cancer cells induced by matriptase overexpression. The data from the study indicate that curcumin exhibits a suppressive effect on prostate cancer cell invasion, tumour growth, and metastasis, in part via the down-regulation of matriptase function [7]. In another study, the anticancer activity of curcumin and genistein combination in human prostate cancer (PC3) cell line with respect to their anti-angiogenic effect has been examined. The combination of both compounds was shown to decrease cell viability, induce apoptosis and cell cycle arrest at G_0 phase in a dose- and time-dependent manner. In order to understand the anti-angiogenic effect of the combination, the authours determined the expression of ARNT and HIF-1α protein levels which were shown to significant decline when compared to the control group and their respective monotherapy-treated groups [1].

The transcriptional activity of the androgen receptor (AR) is modulated by interaction with co-regulators, one of which is β-catenin. The effect of curcumin in inhibiting AR expression has also been elucidated through its role in mediating Wnt/β-catenin signalling pathway with regard to AR/β-catenin interactions. Curcumin induced a significant inhibition of AR expression in a dose-dependent manner as well as its suppression of β-catenin in the nuclear and cytoplasmic extracts and whole cell lysates. Phosphorylation of Akt and glycogen synthase kinase-3β was shown to be attenuated, while phosphorylated β-catenin was increased after curcumin treatment. Cyclin D1 and c-myc, the target genes of the β-catenin/T-cell factor transcriptional complex, were also shown to be decreased; a finding that highlights the effect of curcumin in modulating the Wnt/β-catenin signalling pathway and may thus play a significant role in mediating inhibitory effects on LNCaP prostate cancer cells [10]. The anti-tumour activity of curcumin against androgen-independent prostate cancer cells *in vitro* and the possible mechanism of action have also been investigated. The results showed curcumin to effectively inhibit the proliferation of PC-3 cells *in vitro* with cell cycle arrest at the G_2/M

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interphase. The percentage of apoptotic cells was shown to be significantly higher in curcumin-treated groups than in control group and curcumin was shown to selectively inhibit the activities of NF-κB and AP-1 signalling pathways in PC-3 cells significantly [36].

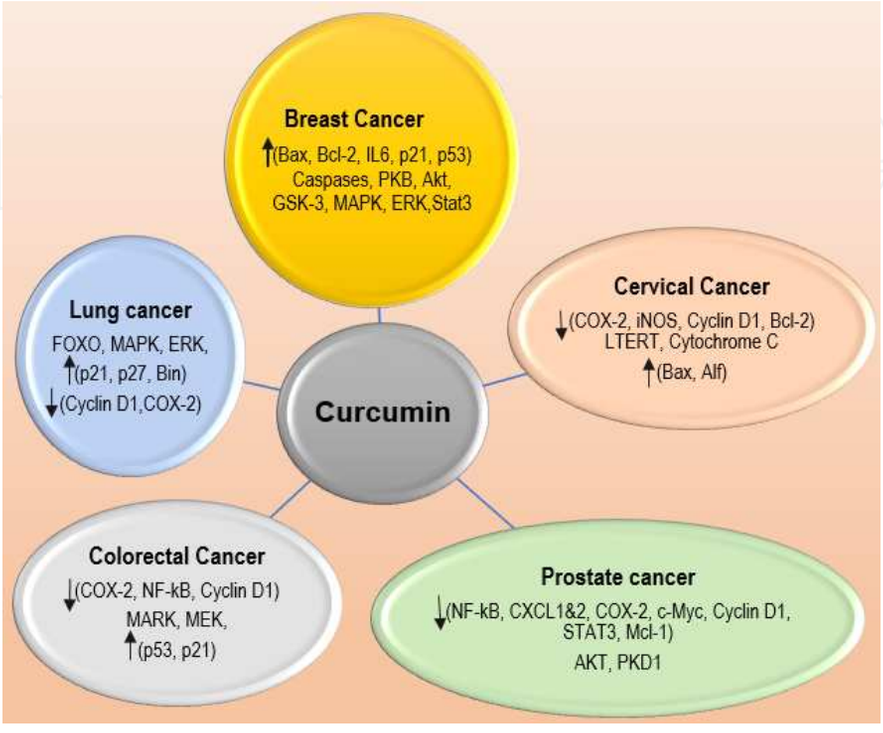

Figure 2. Molecular targets of curcumin and/or its chemically-related analogues and possible mechanisms of action in various types of malignant growths.

The effect of six cyclohexanone analogues of curcumin (Figure 1) has also been investigated for their effects on growth and apoptosis, by evaluating the ability of these compounds to inhibit NF-κB activity in PC-3 human prostate cancer cells. Five out of the six curcumin analogues were shown to have stronger inhibitory effects compared to curcumin on the growth of these cells. They also showed stronger stimulatory effects on apoptosis in PC-3 cells than curcumin, with a more potent inhibition of NF-κB activity than curcumin which correlates well with effects on growth inhibition and apoptosis stimulation in PC-3 cells [62]. Furthermore, the therapeutic potential of a novel poly(lactic-co-glycolic acid)-curcumin nanoparticles (PLGA-Curcumin NPs) for prostate cancer treatment has also been assessed. Findings revealed PLGA-Curcumin NPs to efficiently internalise in prostate cancer cells and release biologically active curcumin in cytosolic compartment of cells for effective therapeutic activity. It was also shown that PLGA-Curcumin NPs can effectively inhibit the proliferation and colony formation ability of prostate cancer cells than free curcumin. PLGA-Curcumin NPs showed superior tumour regression compared to curcumin in xenograft mice. It was also revealed that PLGA-Curcumin NPs inhibit nuclear β-catenin and androgen receptor (AR) expression in cells and in tumour xenograft tissues. Furthermore, it was shown to suppress STAT3 and Akt phosphorylation resulting in apoptosis via inhibition of key anti-apoptotic proteins, Mcl-1, Bcl-xL and caused induction of PARP cleavage [65].).

7. Conclusion

The limiting factor associated with curcumin is its poor solubility in water and likewise when soluble, it is extremely sensitive at physiological pH. However, the potential of curcumin, its derivatives and/or metabolites on cancer cells has been recognised and demonstrated in various cancer cells and its varying mechanisms of action elucidated depending on the tumour cell type. Coupled with this, the pleiotropic property of the curcumin molecule enables it to target the DNA, RNA and enzymes (proteins) within cells thereby eliciting sequential and/or simultaneous therapeutic effects. It is therefore pertinent to strive to refine the properties of curcumin through targeted delivery, tissue distribution and bioavailability in tumour cells in the presence of an adjuvant. These strategies can be achieved through the design and development of nanoparticles, self-assemblies, nanogels, liposome and other formulations that possess characteristics tailored according to specific requirements in order to efficiently harness therapeutic potential of curcumin in the treatment of a variety of malignant growths.

Acknowledgements

This work was made possible by grants from the Medical Research Council (South Africa) awarded to LJM, National Research Foundation, NRF (Thuthuka) awarded to MPM and the University of Limpopo.

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