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Scopes for using curcumin (turmeric) as an effective therapeutic agent against cancer

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Abstract

Curcumin, a polyphenolic compound (diferuloylmethan), is one of the most important ingredients of turmeric (*Curcuma longa*). Its pharmacological properties are known since 600 BC, and it has long been used in Indian medicines such as Ayurveda and Siddha, Chinese medicine and Unani. Although the role of curcumin in the treatment of various ailments has been extensively studied and documented, major attention has been paid to its therapeutic properties against various cancers only during the past three decades. The anti-cancer actions of curcumin are varied and multiple that include, prevention of origin of cancer and curing of cancers of various stages. Its cancer prevention actions include anti-inflammatory and tumor suppression and, its cancer fighting/curing actions include its influence on a variety of metabolic pathway and gene expression. In spite of its well documented anti-cancer properties, it is not being used extensively for the treatments of cancer mainly because of its poor absorption and very low bio-availability in human body systems. In addition, limited and inconclusive clinical trials on its usage against cancer in human, make it ineligible for prescribing as a medicine in the treatment of cancer by the authorities of the conventional medical systems. The present review analyses the various scopes for using curcumin in cancer therapy based on various research findings and latest developments.

Key words: cancer therapy. Curcumin, turmeric,

INTRODUCTION

Cancer, although popularly regarded as a 'disease', actually is not a disease but it is a survival mechanism of the cells that have faced serious threats both from external and internal agents (Andreas, 2008). If we critically go through the origin of cancer cells, one can easily understand as to how the external and internal agencies are responsible for the origin of cancer cells from the normal cells. Free radicals, inflammation, stress, infection, toxins and other physiological insults take their toll, inflicting lethal damage over time that make certain genes of the normal cells to become abnormal and dysregulated, resulting in uncontrolled proliferation in motion. Recent findings reveal that as many as 300 dysregulated genes are involved in the origin and growth of various cancers (Vogelstein and Kinzler, 2004; Gupta *et al*., 2010; Hasima and Aggarwal, 2012). The established cancer cells differ from the normal cells in some unique characters that are named as 'Hallmark characters'. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis. Underlying these hallmarks is genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list— reprogramming of energy metabolism and evading immune destruction (Hanahan, 2011). These hallmark characters are common to all cancer types and responsible for their successful growth and survival. Therefore, targeting cancer requires intervention of these hallmark characters. Each of these hallmark characters involve multiple metabolic functions controlled by hundreds of dysregulated oncogenes as already stated above. This necessitates adopting a multiple targeting therapeutic mechanism for an effective cancer treatment protocol, as attacking only one of these multiple pathways is highly unlikely to be effective (Subash *et al*., 2013). Such treatment should be cost effective and devoid of serious side-effects. Unfortunately, so far, no conventional treatment protocols adopt such multiple targeting therapeutic means in the treatment of cancer. In spite of the fact that cancer is the second leading cause of death in the developed world, we are still in the dark ages in terms of treatment and understanding (Ji, 2012). Obviously the present conventional medical system has failed in bringing fruitful solution for fighting against cancer in spite of huge expenditure for the treatment, and hence it is imperative to seek some alternative drug that is cost effective with multiple targeting functions, attacking many of the 'Hallmark characters' of the cancer cells. Recent findings qualify Curcumin, an important polyphenolic compound present in turmeric, as one such candidate with the above said multiple targeting functions. It is appropriate to quote, "*No cancer has been found that is not affected by curcumin*" (MD Anderson Cancer Center, Texas).

Curcumin as the multiple-targeting therapeutic agent against cancer:

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Curcumin has got a huge potential for developing it into an effective therapeutic agent for fighting against cancer. This is supported by a number of research findings that are pouring during recent years indicating its action against different cancer cells. As on 2012, about 350 peer reviewed studies (Table, 1) support the therapeutic properties of Curcumin against various cancers (Ji, 2012). Number of studies have been added till date on anti-cancer actions of curcumin and are reviewed from time to time (Singh and Aggarwal, 1995; Milacic *et al*., 2008; Bar-Sela *et al*., 2010; Amar, 2010; Darvesha *et al*., 2012; Belinda *et al*., 2013; Rahmani *et al*., 2014; Mehtah *et al*., 2014; Salem *et al*., 2014; Hosseinimehr and Hosseini, 2014; Steffl and Sreenivasan, 2014; Chen, 2015; Devassy *et al*., 2015; Muthu *et al*., 2015). These reviews are of two types – reviews that analyzed the anticancer role of curcumin with reference to a particular cancer type and reviews that deal with cancer in general. Summaries of the important findings of these reviews are presented below.

Findings of some recent review articles on the therapeutic values of curcumin against different cancers:

a. Breast cancer: Belinda *et al*. (2013) in their review considered the evidence for the use of curcumin as a treatment for breast cancer, particularly triple negative breast cancers (lacking ER, PR and HER2) which are resistant to many current treatments. Evidence suggests that curcumin suppresses the growth of breast cancer cells both *in vitro* and *in vivo*. In ER-cell lines curcumin causes apoptosis via a range of mechanisms at concentrations ranging between 1 ìM and 7.6 ìM depending on the cell line and system. They also discussed the development of curcumin derivatives. Many of them showed increased cytotoxicity (less than 1 ìM) and improved pharmacokinetic profiles *in vivo*. The most potent of these compounds developed to date are RL66 and RL71 with IC50 values less than 1 ìM across a range of breast cancer cell lines, decreased metastasis in a xenograft model, decreased angiogenesis markers and improved tumour growth inhibition as compared to curcumin. In a nutshell it is concluded that curcumin and its derivatives could be potential and powerful broad-spectrum therapeutic agent(s) for the treatment of breast cancer.

b. Lung cancer: Mehtah *et al*. (2014) presented an overview of the current *in vitro* and *in vivo* studies of curcumin in lung cancer. They concluded that, curcumin could be an effective adjunct in treating solid organ tumors due to its properties of regulating oncogenes like p53, egr-1, c-myc, bcl-XL, etc.; transcription factors like NF-kB, STAT-3, and AP-1; protein kinases like MAPK; and enzymes like COX and LOX.

c. Liver cancer: Darvesha *et al*. (2012) reviewed the effects of curcumin in preclinical in *vitro* and in *vivo* models of HCC with particular emphasis on its antioxidant, apoptotic and anti-inflammatory effects as well as involvement in various molecular signaling mechanisms. This review also discusses potential challenges involved in the use of curcumin in HCC such as bioavailability, pharmacokinetics, drug delivery as well as paucity of clinical studies. They concluded that curcumin remains a promising chemopreventive and therapeutic agent in the treatment of HCC, though there is the need of thorough study prior to its successful clinical application,

d. Colon cancer: Johnson and Mukhtar (2007) in their mini review on colon cancer, focus on describing the preclinical and clinical evidence of curcumin as a chemopreventive compound in colorectal cancer. They pointed out the robust activity of curcumin in colorectal cancer, and this has led to five phase I clinical trials and found the safety and tolerability of curcumisn in colorectal cancer patients. To date clinical trials using doses up to 8000 mg per day are being carried out. However, a maximum tolerated dose of curcumin has not been identified in humans. The success of these trials has led to the development of phase II trials that are currently enrolling patients. Overwhelming in *vitro* evidence and completed clinical trials suggest that curcumin could be used for the chemoprevention of colon cancer in humans.

In yet another mini review, Amar (2010) concluded that curcumin exhibited multiple activities in the prevention and treatment of colorectal cancer as it down-regulated transcription factor NF-kB, expression of cox-2 (inflammatory mediator) and growth factor receptor EGFR, and inhibited synthesis of prostaglandin E2. On the basis of the evidence it is also suggested that curcumin is safe and well tolerated without any toxicity up to 12g in a single dose.

e. Prostrate cancer: Chen (2015) reviewed the studies on prostrate cancer and reported the prospect of curcumin in treating prostate cancer and its mechanisms of action, and also provided an in-depth overview of current development of curcumin-based anti-prostate cancer agents, their structure and activity relationships, and ends with the syntheses and pharmacokinetic studies of curcumin.

f. Thyroid cancer: Hosseinimehr and Hosseini (2014) reported that curcumin increased the killing effect of 131-I on thyroid cancer cells, while it exerted no toxicity on HFFF2 cells. This result confirms the promising effect of curcumin on the enhancement of therapeutic effects of 131-I in patients.

g. All cancers in general

Bar-Sela *et al*. (2010) and Salem *et al*. (2014) reviewed the clinical evidences including their experience with

Table 1: Number of studies and published articles on the ant-cancer role of curcumin.

Type of Cancer Curcumin has potential value in preventing or treating	Number of peer-reviewed studies supporting its therapeutic properties*
Breast Cancer	58
Colorectal Cancer	23
Colon Cancer	51
Prostate Cancer	42
Pancreatic Cancer	24
Cancers: Drug Resistant	40
Lung Cancer	37
Liver Cancer	27
Cancer Metastasis	32
Skin Cancer	15

* This information is pertaining to February, 2012. Lot many articles have been added subsequently.

(Source: http://www.greenmedinfo.com/blog/does-chemo-radiation-actually-make-cancer-more-malignant?page=2)

Table 2: Modulation of cancer related chemical pathways by the FDA approved cancer drugs and mode of actions of curcumin in the respective pathways.

Name of the FDA drugs that act on cancer cells similar to curcumin.	Mode of action by the drug on cancer cells	Mode of action by the curcumin
Bortezomib and lenalidomide	Inhibit the action of NF-kB, and induce apoptosis in cancer cells	Inhibits both inducible and constitutive activation of NK-kB in various cancer cells. Inhibit proteasome. (Singh and Aggarwal, 1995; Milacic *et al*., 2008)
Infliximab and Adalimumab	Inhibit the action of Tumor necrosis factor alpha (TNF-á) that induces inflammation.	Inhibits production of TNF-á and suppresses the TNF signaling pathways. (Milacic *et al*., 2008; Chan, 1995)
Vorinostat and Romidepsin	Inhibit the activity of Histone deacetylases (HDACs) that regulates cell cycle. Used in the treatment of cutaneous T-cell lymphoma.	Blocking expression of HDACs in Raji cells. (Liu *et al*., 2005)
Gefitinib, cetuximab,erlotinib, panitumumab, lapatinib ditosylate and vandetanib.	Anti-EGFR. EGFR is a protein that is responsible for abnormal cell division of cancer cells.	Inhibits the constitutive activation of both EGFR anf insulin growth factor-1 receptor signaling pathways in colon cancer cells and MCF-7 breast cancer cells. (Reddy *et al*., 2006; Xia et al., 2007).
Trastuzumab, pertusuzumab.	Anti- HER-2 – Another member of EGFR super family.	Tagets HER-2 effectively. (Hong et al., 1999; Patel *et al*., 2010).
Sorafenib tosylate, dasatinib, pazopanib and axitinib	Anti-PDGFR. PRGFR stimulates cell growth and proliferation.	Inhibits PDGFR-induced proliferation of human hepatic myofibroblasts. (Park et al., 2005).
Bevacizumab, sorafenib tosylate, sunitinib malate, temsirolimus, pasopanib and axitinib.	Anti-VGF and Anti-VGFR. Over expression of VGF and VGFR are the biomarkers of angiogenic activity in cancer.	Inhibits both VEGF and VEGFR actions in various cancers. Effective antiangiogenic agent. (Chua et al., 2000; Chadalapaka *et al*., 2008).

Sorafenib tosylate and vermurafenib	Anti-B-RAF. Mutated B-RAF proteins induce cell proliferation in cancer.	Inhibits B-RAF oncogenic activity. (Andreadi *et al.*, 2006).
Temsirolimus and everolimus	Anti-mTOR. mTOR pathway plays a prominent role in growth, proliferation, motility and angiogenesis in cancer cells.	Efficient anti-mTOR agent. (Beevers *et al.*, 2006).
Tamoxifen citrate, toremifene, fuvestrant, and raloxifene.	Anti- ER (Estrogen Receptors). Estrogen stimulates proliferation of cells.	Downregulates ER activity in breast cancer. (Verma *et al.*, 1998).
Anastrozole, letrozole and exemestane.	Aromatase inhibitors. – This enzyme is vital for the production of estrogen.	Downregulates ER activity in breast cancer. (Verma *et al.*, 1998).
Tofacitinib	Inhibits JAK2 pathway action. JAK2 pathway is responsible for groth of cancer cells.	Inhibits JAK2 mRANA expression in leukemia cells. (Blasius *et al.*, 2006).
Dasatinib	Inhibits the action of Src oncoprotein in lyphocytic leukemia and myelocytic leukemia.	Downregulates Src kinase activity.(Leu *et al.*, 2003).
Imetinib, dasatinib, and nilotinib	Inhibit the action of Bcr- Abl oncoproten in myelogenous leukemia.	Downregulates Bcr- Abl oncoproten in human leukemia. (Wu *et al.*, 2003).
Drugs that are cytotoxic. FDA approved more than 32 numbers of such drugs.	Destroy cellular components like DNA, RNA, DNA polymerase, mitotic spindle, microtubules, b-tubulin etc. and induce cell death.	Acts a anti-microtubule agent (Gupta *et al.*, 2006).Binds directly to DNA and RNA and functions as antDNA and antRNA drug.(Gupta *et al.*, 2011).Inhibits DNA polymerase (Mizushina *et al.*, 2005).Induces DNA topoisomerases to trigger death in K562 cancer cells. (Lopez-Lazaro *et al.*, 2007).

Table 3: Regulation of cancer causing epigenetic pathways by curcumin for which no FDA drugs available.

Epigenetic pathway category	Down regulation	Up regulation
Inflammatory biomarkers	NF-kB, MMP-2, MMP-9, STAT3, DUBs, 5LOX, 5-HETE, EZH2, iNOS, IL-6, FAK, COX-2, PYK2, HAT.	
Growth factor signaling	IGF-1R, TGFβ, CDK2,CDK4	P21, p27
Transcription factors	AP-1, AR, STAT1, FOXO, ARNT, HIF-1α, PPARδ, β-catenin, GADD45.	GADD153, Nrf2,
Apoptotic genes	Bax, Bak, Noxa, Bim, Caspase8, PUMA, BID,	XIAP, c-FLIP, Survinin, Bcl-xL, Bcl-2, IAP-1, IAP-2,
Oncoproteins	c-Met, c-Myc, N-Myc, Ras, Fos, Mdm2.	
Protein kinases	P13-K, AKT, GSK3, PKC, PKA, JNK, p38, MAPK, p-ERK1/2	AMPK
Tumor suppressor genes		P53, PTEN, Rb.

Inflammatory biomarkers : NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; STAT3, signal transducer and activator; DUBs, deubiquitinating enzymes; 5-LOX, 5-lipoxygenase; 5-HETE, 5-hydroxy-eicosatetraenoic acid; EZH2, enhancer of zeste homolog 2; iNOS, inducible nitric oxide synthase; IL-6, interleukin-6; FAK, focal adhesion kinase; COX-2, cyclooxygenase-2; PYK2, proline-rich tyrosine kinase; HAT, histone acetyltransferases;

Growth factor signaling: IGF-1R, insulin-like growth factor-1 receptor; TGF-β, transforming growth factor-β; CDK2, cyclin-dependent kinase 2; CDK4, cyclin-dependent kinase 4;

Transcription factors: AP-1, activator protein 1; AR, androgen receptor; STAT1, signal transducer and activator or transcription 1; FOXO, forkhead box O; ARNT, aryl hydrocarbon receptor nuclear translocator; HIF-1α, hypoxia-inducible factor-1alpha; PPARδ, peroxisome proliferator-activated receptorδ; GADD45, growth arrest and DNA damage gene 45; GADD153, growth arrest and DNA damage-inducible gene 153; Nrf2, NF-E2 related factor 2;

Apoptotic genes: Bax, B-cell lymphoma 2-associated X protein; Bak, B-cell lymphoma 2 homologous antagonist/killer; Noxa, BH3-only proapoptotic protein; Bim, BH3-only proapoptotic protein; PUMA, p53 upregulated modulator or apoptosis; BID, BH3 interacting-domain death agonist; XIAP, X-linked inhibitor of apoptosis protein. c-FLIP, cellular FLICE-inhibitory protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; IAP-1, inhibitor of apoptosis protein 1; IAP-2, inhibitor of apoptosis protein 2;

Protein kinases: PI3-K, phosphotidylinositol-3-kinase; PKA, protein kinase A; PKC, protein kinase C; AKT, protein kinase B; GSK3, glycogen synthase kinase 3; JNK, cJun N-terminal kinase; MAPK, mitogen-activated protein kinase; p-ERK1/2, phosphorylated extracellular signal-regulated protein kinases 1 and 2; AMPK, AMP-activated protein

Tumor suppressor genes: PTEN, phosphatase and tensin homolog; Rb, retinoblastoma

Table 4: Therapeutic role of curcumin on multidrug resistance cancer cells.

Resistant cancer type	Mode of action by Curcumin and reference number
Oxaliplatin resistance HCT116 colorectal cancer	Curcumin enhanced the cytotoxicity of oxaliplatin in oxaliplatin resistance HCT116 colorectal cancer cells (Howells *et al*., 2011).
Gemcitabine-resistant pancreatic cancer.	Synergic effect with gemcitabine-based chemotherapy (Kanai *et al*., 2011).
Human prostate cancer cell lines PC3	Chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway enhanced the cytotoxic effects of gemcitabine.(Li *et al*., 2007).
Gefitinib resistant Non-small cell lung cancer cells (NSCLC).Adjuvant for gefitinib therapy in lung adenocarcinoma	Curcumin potentiates antitumor activity of gefitinib in cell lines and xenograft mice model of NSCLC through inhibition of proliferation, EGFR phosphorylation, and induction EGFR ubiquitination and apoptosis. In addition, curcumin attenuates gefitinib-induced gastrointestinal adverse effects via altering p38 activation (Lee *et al*., 2011).
Cisplatin-resistant CAR human oral cancer cells	Apoptotic cell death through regulation of the function of MDR1 and reactive oxygen species (Chang et al., 2013).
Mediates chemosensitization to 5-fluorouracil in chemoresistant colorectal cancer.	Curcumin-mediated sensitization to 5FU-related chemoresistance through suppression of EMT in 5FUR cells via upregulation of EMT-suppressive miRNAs (Toden *et al*.,2015).
Cisplatin and oxaliplatin resistant ovarian cancer cells	Synergism in inducing cancer cell death. More effective when curcumin was administered first followed by cisplatin / oxaliplatin 2 hours later (Nessa *et al*., 2012).
Doxorubicin (DOX)-sensitive and resistant MCF-7 cells	Curcumin and EGCG in combination could enhance the toxicity of DOX and increase the intracellular level of DOX in resistant MCF-7 cells (Wang et al., 2014).
Multidrug resistance proteins MRP1 and MRP2	Curcumin clearly inhibits both MRP1- and MRP2-mediated transport, but the glutathione-dependent metabolism of curcumin plays a crucial role in the ultimate level of inhibition of MRP-mediated transport (Wortelboer *et al*., 2003).
Multidrug resistant (MDR) human gastric carcinoma cell line SGC7901/VCR.	Curcumin can reverse the MDR of the human gastric carcinoma SGC7901/VCR cell line. This might be associated with decreased P-gp function and expression, and the promotion of caspase-3 activation in MDR cells (Tang *et al*., 2005).
MDR in non-small cell lung carcinoma cell line (NSCLC)	Sulfinosine and curcumin caused perturbations in cell cycle distribution in the NCI-H460/R cell line. The combination of the two drugs induced a more pronounced cell cycle arrest in S and G(2)/M in NCI-H460/R cells (Andjelkovic *et al*., 2008).

Multidrug-resistant L1210/Adr cells	Curcumin reversed the MDR of the L1210/Adr cells. due to the suppression of P-gp expression via the inhibition of the PI3K/Akt/NF-kappa B signaling pathway (Choi *et al*., 2008).
Chemoresistant ovarian cancer cell lines SKOV3 and ES-	Preincubating cells with curcumin at low doses prior to treating with Apo2L/TRAIL resulted in markedly enhanced cell death. The combined treatment of curcumin and Apo2L/TRAIL resulted in activation of both the extrinsic, receptor-mediated apoptotic pathway (cleavage of caspase-8) and the intrinsic, mitochondria-mediated apoptotic pathway (cleavage of caspase-9) (Wahl *et al*., 2007).
Apoptosis-resistant Bcr-Abl-expressing cells of myeloid leukemia	Curcumin can overcome the broad resistance to cell death caused by expression of Bcr-Abl by strongly inhibiting cell proliferation and affecting cell viability by inducing apoptotic symptoms (Wolanin *et al*., 2006).
Mitomycin C (MMC) associated side effects in 4 breast cancer.	MMC and curcumin together synergistically enhanced apoptosis in MCF-7 cells and the apoptosis most likely resulted from both the activation of caspases and modulation of bcl-2/bax expression (Zhou *et al*., 2011).
Triple negative breast cancer cell lines (MDA-MB-231 and MD-MB-468)	Suppression of the FABP5/ PPARβ/δ pathway by curcumin sensitizes retinoic acid resistant triple negative breast cancer cells to retinoic acid mediated growth suppression (Thulasiraman *et al*., 2014).
Cisplatin-resistant human ovarian cancer cells	Curcumin inhibits the proliferation of cisplatin-resistant ovarian cancer cells through the induction of superoxide generation, G(2)/M arrest, and apoptosis (Weir *et al*., 2007).
Melanoma cells with mutant p53, strongly resistant to conventional chemotherapy,	Curcumin blocks the NF-kappaB cell survival pathway and suppresses the apoptotic inhibitor, XIAP (Bush *et al*., 2001).
Multidrug-resistant CEM (P-gp4) and LoVo(P-gp4) cells	Curcumin induces caspase-3-independent apoptosis (Piwocka *et al*., 2002). .
Multidrug-resistant (MDR) variant of the MCF-7 breast cancer cell line.	Curcumin produced early reductions in the amounts of relevant gene transcripts (Labbozzetta *et al*., 2009).
Multidrug resistance associated protein 1 (MRP1) in retino blastoma (RB) cell lines	Curcumin's interaction with the substrate binding site of MRP1 (Sreenivasan *et al*., 2012).
Multidrug resistance1 (MDR1) gene which encodes P-glycoprotein (Pgp)	Curcumin decreased MDR1 mRNA level in patient leukemic cells, especially in high level of MDR1 gene groups (Anuchapreeda *et al*., 2006).
Multi-drug resistance-associated protein 5 in pancreatic cancer cells.	Curcumin as an inhibitor of MRP5 may be useful in the reversal of multi-drug resistance in pancreatic cancer chemotherapy (Li *et al*., 2011).
Multidrug-resistant cell line K562/A02	It could enhance the sensitivity of K562/A02 cells to chemotherapeutic drugs and the mechanism might be associated with inhibiting P-gp-mediated drug efflux and increasing of intracellular concentration of chemotherapeutic drugs (Huang *et al*., 2010)
Multidrug resistance in the Y79 retinoblastoma cell line.	Curcumin modulated the expression of LRP in the Y79 retinoblastoma cell line (Thiyagarajan *et al*., 2009).
Bladder cancer management often suffers from toxicity and resistance concerns.	Curcumin induces hypomethylation of the miR-203 promoter and subsequent upregulation of miR-203 expression. This leads to downregulation of miR-203 target genes Akt2 and Src that culminates in decreased proliferation and increased apoptosis of bladder cancer cells (Saini *et al*., 2011).
Cells of the HL-60-derived HCW-2 line highly resistant to apoptosis	Curcumin acts on HCW-2 cells by inhibiting the expression of survivin, a modulator of cell division and apoptosis in cancer (Magalska *et al*., 2006).
PC cell resistance to taxane.	Curcumin decreases HRPC aggressive proliferation and potentiate activity of taxane therapy (Cabrespine-Faugeras *et al*., 2010).

Multidrug resistance (MDR) reversal of K562/A02 cell line	Reverse the multidrug resistance of K562/A02 cells and decrease the expression and function of P-gp (Chang *et al.*, 2006).
Multidrug-resistant human lung adenocarcinoma cells - A549/DDP	Significantly downregulated the expression of miR-186 in A549/DDP and induced apoptosis (Zhang *et al.*, 2010).
Tamoxifen resistant G361 malignant human melanoma cell lines	Significant induction of autophagy along with apoptosis following the combined treatment of curcumin and tamoxifen and non-cancerous cells are unaffected by the combination of these non-toxic compounds (Chatterjee *et al.*, 2011).
Multidrug resistance of MOLP-2/R - multiple myeloma	The possible mechanisms include (1) reduction of DNA damage repair and stimulation of apoptosis of tumor cells through inhibition of FA/BRCA pathway, which is important for DNA repair, and achievement of high concentration in target cells (Xiao *et al.*, 2010).
Multi-drug (doxorubicin) resistant of human osteosarcoma cell line model (U-2OS/ADM)	Curcumin increases the accumulation of Rh-123 and increase the cytotoxicity of Adriamycin to U-2OS/ADM cells in a dose-dependent manner (Xiao and wang, 2011).
Malignant gliomas a class of brain tumors that are resistant to radiation and chemotherapeutic drugs	Curcumin-sensitized glioma cells to several clinically utilized chemotherapeutic agents (cisplatin, etoposide, camptothecin, and doxorubicin) and radiation, effects correlated with reduced expression of bcl-2 and IAP family members as well as DNA repair enzymes (MGMT, DNA-PK, Ku70, Ku80, and ERCC-1) (Dhandapani *et al.*, 2007).
Human lymphoma cell line HT/CTX with drug resistance	Curcumin could enhance toxicity of CTX on HT/CTX cells (75). through inhibition of FA/BRCA pathway which was realized by suppression of FANCD2 monoubiquitination. The curcumin combined with CTX could increase apoptosis inducing effect on HT/CTX cells, while the curcumin or CTX alone did not showed this effect (Xiao and zhang, 2008).
Drug resistant SKOV3(TR) human ovarian adenocarcinoma cells.	CUR administration was shown to inhibit NFkappaB activity and down regulate P-glycoprotein expression in resistant cells. Combination PTX and CUR therapy, especially when administered in the nanoemulsion formulations, was very effective in enhancing the cytotoxicity in wild-type and resistant cells by promoting the apoptotic response (Ganta and Amiji, 2009).
Colon cancer stem cells (CSCs) that are resistant to conventional chemotherapy. 5-FU plus oxaliplatin (FOLFOX)	Treatment of FOLFOX-surviving colon cancer cells with either curcumin alone or together with FOLFOX resulted in a marked reduction in CSCs, as evidenced by the decreased expression of CD44 and CD166 as well as EGFR and by their ability to form anchorage-dependent colonies (Yu *et al.*, 2009). Addition of curcumin to oxaliplatin/5-FU enhanced anti-proliferative and pro-apoptotic effects in a proportion of patient-derived explants, whilst reducing expression of stem cell-associated markers ALDH and CD133 (Mark *et al.*, 2015).Curcumin suppressed EMT (epithelial-mesenchymal transition) in 5FUR cells by down regulating BMI1, SUZ12 and EZH2 transcripts, key mediators of cancer stemness-related polycomb repressive complex subunits.
Multidrug resistance to chemotherapy in HEK293 cells	The modulatory effect of curcuminoids on MRP1 (ABCC1) function was confirmed by the inhibition of efflux of two fluorescent substrates, calcein-AM and fluo4-AM (Chearwae *et al.*, 2006).
Drug resistance to long-term exposure to adriamycin in K562 cells	Curcuminoids inhibit the adriamycin-induced increase of NF-êB nuclear translocation and activation. curcuminoids have the potency to block the upregulation of P-gp and its mRNA induced by short- and long-term exposure to adriamycin (Xu *et al.*, 2013).
Drug resistance KB-V-1, MCF7AdrVp3000 and MRP1-HEK 293 cells to vinblastine, mitoxantrone and etoposide	Tetrahydrocurcumin (THC) inhibits the efflux function of P-gp, MXR and MRP1 and it is able to extend the MDR reversing activity of curcuminoids in vivo (Limtrakul *et al.*, 2007).

curcumin as a chemopreventive and therapeutic agent and the *in vitro* background results. They described the main physicochemical properties of curcumin, including its chemical structure, stability, and degradation products as a function of pH and temperature. They also described the proposed mechanisms by which curcumin exhibited anti-cancer activity. Finally, they reviewed the various approaches that have been studied to enhance the solubility and bioavailasbility of curcumin, including the preparation of co-crystals and the development of delivery systems based on liposomes, micelles, exosomes, nanoparticles and dendrimers. Rahmani *et al*. (2014) in their review critically analized the 12 different molecular pathways' modulation influenced by curcumin, supported by evidences from the results of several clinical trials with curcumin; and also analyzed the toxicity level of curcumin, discussed the role of analogue/derivatives of curcumin and finally critically analized the bioavailability aspects of curcumin. Devassy *et al*. (2015) in their review critically analyzed the reason that prevent the Health Canada from grant of approval for the cancer risk reduction claim for curcumin within the current regulatory framework. According to them the scientific evidences substantiating the positive correlation between curcumin consumption and a reduction in the risk of cancer are not suitably designed human clinical trials that clearly demonstrate any direct effect of curcumin on cancer markers.

There are many other research articles focusing the anti-cancer action of curcumin in various cell lines. Only important review articles highlighting the latest and new findings have been considered for discussion in this review. On the basis of the perusal of the literature it is concluded that curcumin is the potential candidate in the prevention of cancer through modulation of multiple molecular pathways. The multi targeting properties of curcumin have proved the application of curcumin against numerous cancer types in human clinical trials (Muthu *et al*.,2015).

Specialty of curcumin as an effective therapeutic agent in cancer treatment:

It is well established that the curcumin has got multifarious therapeutic potentials against various cancers. In addition, it has got some unique and special characters that overrule the therapeutic characters of many of the conventional medicines currently used in cancer treatment. Such specialties are grouped and discussed in the following headings:

a. Therapeutic properties of curcumin similar to conventional medicines against cancers:

b. Therapeutic properties of curcumin for which no conventional medicines available.

c. Therapeutic role of curcumin against the drug resistant cancer cells.

d. Effect of curcumin on normal cells.

a. Therapeutic properties of curcumin similar to conventional medicines against cancers:

Most of the conventional medicines currently used in the treatment of cancers are put into use after the approval of the FDA (Federal Drug agency) of the US. Since 1952, 89 drugs have been approved by the FDA for the treatment of various cancer types (Hasima and Aggarwal, 2012) and are being used all over the world.

This section highlights cancer-related targets that are modulated by curcumin as well as one or more FDA-approved drugs. These drugs are grouped under the following categories: Inflammatory biomarkers, Modulation of growth factors and their cell signaling pathway, Modulation of protein kinases and protein phosphatases, Upregulation of tumor suppressor genes, Modulation of various transcription factors, Modulation of proapoptotic pathways and Modulation of oncoproteins. Actions of the drugs on one or more of those pathways and the mode actions of curcumin in the respective pathways are briefly explained and presented in Table, 2.

b. Therapeutic properties of curcumin for which no conventional medicines available.

As stated in the previous paragraph most of the therapeutic properties of curcumin are very similar and in some cases more effective when compared to many of the FDA approved cancer drugs. Curcumin's specialty does not stop with that. There are many more therapeutic properties of curcumin for which no drugs have been developed so far. As days passes many new therapeutic properties will be added to the credit of curcumin. Hasima and Aggarwal (2012) listed out many epigenetic pathways that are targeted by curcumin for which there are no FDA approved drugs. They are presented in Table 3.

C Therapeutic properties of curcumin on multidrug resistant cancer cells:

Unlike many conventional drugs for cancer treatments, curcumin does not have any side-effects. On the other hand, it not only makes the MDR (Multi-drug resistant) cells to respond to many conventional medicines but also seems to increase the effectiveness of these medicines by acting in a synergetic manner. Further, it minimizes the side-effects caused by the conventional drugs. In some cases, curcumin helps to reduce the quantum of some costly conventional medicine by performing the function of the respective medicines effectively but in a cheaper way. All the above mentioned therapeutic actions are briefly presented in Table 4.

d. Effect of curcumin on normal cells:

Unlike many of the conventional cancer drugs that have many harmful effects on normal cells, curcumin kills only cancer cells and does not affect the normal cells.

The reason for this is not fully understood. However, this differential action of curcumin is attributed to some specific characters of cancer cells. The uptake of curcumin is higher in tumer cells than the normal cells (Kunwar *et al*., 2008). Such higher uptake may be due to lower availability of glutathione in tumor cells than the normal cells that makes them more sensitive to curcumin (Syng-Ai *et al*., 2004). Unlike normal cells, most tumor cells express constitutively active NF-kB and thus mediate their survival (Shishodia *et al*., 2005). On the other hand, curcumin suppresses the actions of NK-kB-regulated gene products as evidenced from large number of studies. Thus, the differential actions of curcumin on cancer cells may be attributed to some differential / abnormal characters of the cancer cells that differentiate them from normal cells.

Delivery, Bioavailability, Absorption and Metabolism of Curcumin:

In spite of all the above positive therapeutic qualities of curcumin, as evidenced from large number of research findings, it is not yet officially declared or approved as a therapeutic agent to be used against cancer by the conventional medical system. The major reason behind this is the low bioavailability of curcumin (Anand *et al*., 2007). The recent studies emphasized the need for a technology that could improve the bioavailability of curcumin in order to harvest the maximum potential of curcumin to fighting against cancer (Prasad *et al*., 2014).

Moreover, paucity of suitably designed human clinical trials that clearly demonstrate any direct effect of curcumin on cancer markers may prevent from approving a cancer risk reduction claim for curcumin within the current regulatory framework (Gupta *et al*., 2011). However, a large number of ongoing clinical trials and completed clinical trials support the value of curcumin in cancer treatment (Ji *et al*., 2012).

Recent technological advances in improving the bioavailability of curcumin:

The major factors that affect the bio-avilability of curcumin are: serum concentration, tissue distribution, rapid metabolism and short half-life. Therefore, these factors are addressed to improve the bio-availability (Kim et al., 2011; Prasad, *et al*., 2014). The various methods and formulations through which attempts were made to solve these problems include, Unformulated curcumin, Nanocurcumin, Polylactic-co-glycolic acid (PLGC), Liposomal encaptulation, Cyclodextrin (CD) and Peperine. There are many review articles that highlight the recent findings on the composition and effective use of these methods in the treatment of cancers (Anand *et al*., 2007; Kim *et al*., 2011; Ji *et al*., 2012; Liu *et al*., 2013; Ghalandarlaki *et al*., 2014; Hani and Shivakumar, 2014; Lee *et al*., 2014; Naksuriya et al., 2014; Prasad *et al*., 2014).

Methods of using unformulated curcumin for improved bio-availability in human beings are also available. The unformulated curcumin used were either in the form of turmeric powder (Cheng *et al*., 2001) or concentrated curcumin (Sharma *et al*., 2001). Sharma *et al*. (2001) in their study with colorectal cancer patients concluded that turmeric extract could be administered safely to patients at doses of up to 2.2 g daily, equivalent to 180 mg of curcumin. Dhillon *et al*. (2008) reported that oral curcumin was well tolerated, despite its limited absorption, and also had biological activity in some patients with pancreatic cancers.

Use of nanoparticle formulations is emerging as useful alternative that has been shown to deliver therapeutic concentrations of curcumin. Being this technology is a recently developed one, not much of research findings are available. However, several review articles have appeared recently on this novel technology highlighting the effective utility of curcumin in treating various ailments especially cancer (Yallapu *et al*., 2010; Bansal *et al*., 2011; Mimeault *et al*., 2011; Sasaki *et al*., 2011; Yallapu *et al*., 2012; Murali *et al*., 2013; Kanai, 2014; Shehzad *et al*., 2014; Muthu *et al*., 2015). These reviews highlighted that the nanotechnology not only improved the bioavailabilty but also increased the therapeutic effects of curcumin. Using this technology, attempts have been made to treat various cancers using curcumin.

Yallapu *et al*. (2012) prepared encapsulated curcumin in poly lactic-co-glycolide (PLGA) (biodegradable polymer) nano particles in the presence of poly vinyl alcohol and poly L-lysine stabilizers, using a nano-precipitation technique. An optimized curcumin nano-formulation has demonstrated two and six fold increase in the cellular uptake in cisplatin resistant A2780CP ovarian and metastatic MDA-MB-231 breast cancer cells respectively when compared to free curcumin. Results of their study suggest that therapeutic efficacy of curcumin may be enhanced by such PLGA nanoparticle formulations, and furthermore tumor specific targeted delivery of curcumin is made feasible by coupling of anti-cancer antibody to the NPs.

Kanai (2014) used one of the new varieties of nanoparticle-based curcumin namely 'Theracurmin' for the treatment of pancreatic cancer. He found that there was increase in the bioavailability, and concluded that THERACURMIN® may prolong the overall survival of patients with pancreatic cancer through QOL improvements. Piperine, a major natural component of black pepper, has been used widely with curcumin to increase the bio-availability of curcumin. Researchers found that, in humans, bioavailability of curcumin was increased by 2000% at 45 minutes after co-administrating curcumin orally with piperine. This study further revealed that piperine enhanced the serum concentration, extant of absorption and bioavailability

of curcumin without any adverse effect (Shoba *et al.,* 1998). These findings led to further studies on using curcumin-piperine loaded nanoparticulates to enhance the bioavailability still further (Moorthi *et al.,* 2012). Consequently, Moorthy and Kathiresan (2013) proposed a dual drug-loaded nanoparticulate combination therapy containing curcumin and a bio-enhancer such as piperine, quercetin or silibinin, which could significantly overcome the multidrug resistance and other limitations including lack of cancer cell targeting, lack of aqueous solubility, rapid systemic clearance, intestinal metabolism and hepatic metabolism, and was expected to enhance the efficacy of curcumin in the treatment of multidrug-resistant cancers. The proposed dual drug-loaded nanoparticulate combination seems to have potential in treating multidrug-resistant cancers. Recently, Tu *et al.* (2014) worked out the preparation, characterization and evaluation of curcumin - piperine-loaded cubsome nanoparticles in order to improve oral bioavailability and tissue distribution of curcumin. The pharmacokinetic test revealed that the cubosome could improve the oral bioavailability significantly compared to the suspension of curcumin with piperine.

In order to establish the use of curcumin as an approved therapeutic agent against various cancers, many clinical trials have been taken up and their findings were published (Ji *et al,*. 2012; Shehzad *et al.,* 2014). Muthu. *et al*. (2015) in their recent review tabulated various clinical trials that have been taken up using curcumin for cancer treatment along with their findings. They concluded that, clinical trials with curcumin indicate safety, tolerability, non-toxicity (even up to doses of 8000 mg/ day) and efficacy. These studies provide a solid foundation for more well-controlled studies in larger cohorts as well as open avenues for future drug development.

Apart from these completed clinical trials, there are many other ongoing clinical trials to establish the efficacy of curcumin and to recommend it in the cancer treatment (Krishnakumar *et al.,* 2012; Kanai *et al.,* 2013). The results of these trials may enlighten the utility of the curcumin as an effective cancer drug.

CONCLUSIONS:

Voluminous research findings both *in vitro* and *in vivo* together with clinical trials conducted over the past few decades are more than enough to substantiate the potential of curcumin as an anti-cancer agent. Many research findings established that curcumin has got many therapeutic properties that are similar to many conventional medicines currently used in cancer treatments. What is even more amazing is that it has been repeatedly demonstrated to possess both chemoprotective and chemosensitizing properties, and also it has profound radioprotective and radiosensitizing properties as evidenced by lot of research articles (Ji, 2012). Considering the safety and least side-effects, curcumin excels over these conventional drugs. Apart from these advantages, curcumin has got so many other therapeutic properties against cancer for which no drugs in conventional treatments are available. The problem of poor bio-availability that has been repeatedly pointed out in most of the research findings as the major drawback in using it as an effective drug, is also solved to a greater extent by the application of nanotechnology during the recent years. This ensured greater delivery and effective bio-availability of curcumin in cancer therapy. Many of the phase-I and phase – II clinical trials reported the safety, tolerability, non-toxicity and efficacy of curcumin in various forms. However, pending further advanced clinical trial studies that fulfill the quality control needs / criteria for declaring it as a drug against cancer makes that it could not be legally considered as a drug for cancer treatment by the conventional medical system. But, this will not hinder the use of curcumin and its products in the treatment of cancer as a food supplement as, improper food and deficiencies of many food supplements play a major role in the origin and growth of cancer (Andreas, 2008). As long as curcumin in the form of turmeric was in usage as an important drug in the traditional medical systems such as Ayurveda, Sidda and Chinese for the past several centuries, and the modern medical research findings established its potential therapeutic properties, the scopes for using curcumin as an effective therapeutic agent against cancer is considered as very prospective. In addition, the recent developments on the technology of producing higher bio-available forms of curcumin further improve its prospective. Many such highly bio-available curcumin food supplement products are patented and marketed now based on established human clinical research studies (Antony *et al.,* 2008; Krishnakumar *et al*., 2012; Kanai *et al,* 2013; Thierry *et al.,* 2014). It is appropriate to conclude here with the concern of Ji (2012), *'Given this growing and compelling body of research, should not curcumin be considered for use in cancer treatment? And if not as a first-line treatment, then at the very least as an adjuvant in integrative cancer care?'*

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