Table 1. *In vitro* activity of Curcumin (Cur) alone and in combination

Cancer type	Cell line	Concentration in μM of Cur and other agents if any	*Cell viability as % of control	Ref. No.
Breast cancer	MCF-7	2.7 Cur	9 ± 1	[53]
	$MCF\text{-}7_{ADR}$ (Adriamycin-Resistant)	2.7 Cur	15 ± 6	
	BT-20	2.7 Cur	1 ± 0	
	$BT\text{-}20_{TNF}$ (Tumor Necrosis Factor-Resistant)	2.7 Cur	8 ± 0	
	MCF-10A (Normal Mammary Epithelial)	55.0 ± 3.53 Cur	50	[54]
	MCF-7/TH (Multidrug-Resistant)	17.5 ± 1.76 Cur	50	
	MCF-7	109 ± 1.915 Cur	50	[55]
	MCF-7/Dox (Doxorubicin-Resistant)	80 ± 2.39 Cur	50	
	MCF-7/Dox (Doxorubicin-Resistant)	7 Doxorubicin	50	
	MCF-7/Dox (Doxorubicin-Resistant)	40 Cur + 3.5 Doxorubicin	80	
	MCF-7	9.7 Cur	50	[56]
	MCF-7/LCC2 (Antiestrogen-Resistant)	12.2 Cur	50	
	MCF-7/LCC9 (Antiestrogen-Resistant)	11.34 Cur	50	
	MCF-7	7.5 Cur + PDT	50	[58]
	MCF-7/ADM (Adriamycin-Resistant)	7.5 Cur + PDT	50	
Colorectal Cancer	HCT116	9 Cur	50	[59]
	HCT116R (5 FU-Resistant)	5 Cur	50	
	HCT116	5 5-FU	50	
	HCT116R (5 FU-Resistant)	10 5-FU	>80	
	HCT116	5 Cur + 0.1 5-FU	50	
	HCT116R (5 FU-Resistant)	5 Cur + 2 5-FU	50	
	HCT116	20 Cur	50	[60]
	HCT116+ch3 (Complemented with chromosome 3)	5 Cur	50	
	HCT116	5 5-FU	50	
	HCT116+ch3 (Complemented with chromosome 3)	1 5-FU	50	
	HCT116	5 Cur + 1 5-FU	50	
	HCT116+ch3 (Complemented with chromosome 3)	5 Cur + 0.1 5-FU	50	
	HT29	8.5±1.6 Oxaliplatin	50	[61]
	HT29	9 ± 1.4 Cur	50	
	HT29	4.6 ± 1.1 Cur + 3.24 ± 0.7 Oxaliplatin	50	
	HTOXAR3 (Oxaliplatin Resistant Derived Sub-line of HT29)	8.3 ± 0.8 Cur	50	
	HTOXAR3 (Oxaliplatin Resistant Derived Sub-line of HT29)	30.2 ± 4.2 Oxaliplatin	50	
	HTOXAR3 (Oxaliplatin Resistant Derived Sub-line of HT29)	10 Cur + 10.6 ± 2.2 Oxaliplatin	50	
Leukemia	KG1a	35.7 Cur	50	[62]
	Kasumi-1	23.5 Cur	50	
	HL60	30 Cur	50	[63]
Lung Cancer	A549	1.89 Doxorubicin	50	[65]
	A549	2.6 Cur + 1.1 Adriamycin	50	
	A549/ADR (Adriamycin-Resistant)	69.7 Doxorubicin	50	
	A549/ADR (Adriamycin-Resistant)	98.5 Cur + 41.7 Adriamycin	50	
Prostate Cancer	C4-2B	0.59 Docetaxel	50	[69]
	C4-2B	30 Nelfinavir	50	
	C4-2B	59 Cur	50	
	C4-2B	0.01 Docetaxel+5 Nelfinavir+5 Cur	ffi30	
	PC3	21.4 ± 0.8 Cur	50	[70]
	PC3 Docetaxel-Resistant	20.9 ± 0.3 Cur	50	
	DU145	19.5 ± 1.1 Cur	50	
	DU145 Docetaxel-Resistant	27.1 ± 1.4 Cur	50	

*% Cell viability as compared to control (control is 0% inhibition)

characteristic properties of CSCs make them a bigger challenge than other neoplastic cells. Severe combined immunodeficiency disease (SCID) mice show new tumor growth when transplanted with CSCs[74]. An understanding of CSCs with respect to their properties, which are common to other cells and differentiating characters, which make them distinguished targets can lead to sophisticated strategies to deal with the CSCs. It has been shown that CSCs also show some regularity pathways similar to normal cells like Wnt/β-catenin[75,76], Sonic Hedgehog (Hh)[77,78], Notch[76], and Hippo[79,80] Signaling pathways.

Curcumin against Wnt/β-catenin pathway

The role of the Wnt signaling pathway in cell multiplication and differentiation[81,82] is well established. The irregular activation of Wnt pathway has been implicated in human cancer because of anomalous increase in the nuclear concentration of β-catenin and consequential activation of cancer associated genes[83-85]. β-catenin has been linked to various cancers including colorectal carcinoma, non-small cell lung cancer, breast cancer and prostate cancer[86]. Regulation of hyper-activated Wnt signally is an important strategy to control cancer involving this pathway. Human non-small cell lung cancer (NSCLC) cell line A427 and A549 on treatment with curcumin up-regulated micro RNA miR-192-5p and inhibited the cell growth and migration with the deactivation of Wnt/β-catenin pathway[87]. Similar deactivation by curcumin has been reported in medulloblastoma through regulation of the Wnt/β-catenin pathway with down-regulation of β-catenin and Cyclin D1[88]. Curcumin induced apoptosis in HCT-116 cells and derived cell lines without p53 or p21 genes at 20 μM with 67% to 88% cells arrested in G2/M phase and curcumin pretreatment inhibited transcriptional activity of the β-catenin/Tcf-Lef complex and activated Caspase-3[89]. Mechansitic insights from other investigations have consolidated the understanding of role of curcumin in inhibition of Wnt/β-catenin pathways in various cancers[90,91].

Curcumin against hedgehog signaling pathway

Sonic Hedgehog (SHH) signaling pathway involves transduction of signals directed at regulation of growth of multicellular organisms[92,93]. The growth and development in an embryo is a complex phenomenon and impaired SHH signaling is known to reflect in birth defects and complications pertaining to cancer growth[94] in mammals.

Curcumin has been shown to regulate GLI1 mRNA and GLI1 reporter activity in prostate cancer cell lines and *in vivo* model and GLI1 is known to be an important transcription factor in Hedgehog pathway[95]. Significant outcomes were noticed in transforming growth factor-β1(TGF-β1)-stimulated PANC-1 cell lines, on treatment with curcumin (30 μM/mL), which not only inhibited the cell proliferation, invasion and migration but also reversed the EMT caused by TGF-β1. The down-regulated expressions of Shh and GLI1 in PANC-1 cells can be attributed to inhibition of Shh Signaling pathway by curcumin[94]. Many other studies on molecular mechanism of action have reported the reversal of EMT by curcumin through inhibition of Shh pathway[96-98]. Bladder cancer stem cells (BCSCs) UM-UC-3 and EJ, showed deactivation of the sonic hedgehog (Shh) signaling on treatment with 50 μM concentration of curcumin and increase in pro-apoptotic expressions of Bax and cleaved Caspase-3[99]. At the same concentration of curcumin, these cells considerably lost the capacity to form spheres and a higher percentage of cells was found in the G_0/G_1 phase. Shh protein and other downstream expressions in the hedgehog pathway like GLI1 and PTCH1, were found to be decreased in human primary medulloblastoma cells on treatment with curcumin[100].

Curcumin against notch signaling pathway

Notch signaling pathway is directly involved with cell proliferation and differentiation. Aberrant changes in this pathway lead to cancer and related features including drug resistance and tumor growth[101,102]. Gamma (γ)-secretase (GS) is an important component of Notch signaling and its inhibition is implicated in suppression of cancer growth, inhibition of tumor formation and subjugation of cancer stem cells[103,104]. Curcumin has been shown to restrain Notch pathway in esophageal cancer by suppressing GS components

Nicastrin and Presenilin-1[105]. Notch signaling is known for enabling self-renewal and survival of cancer stem cells[106]. Curcumin has been shown to down-regulate the activated Notch-1 signaling human umbilical vein endothelial cells (HUVECs) exposed to hydrogen peroxide-induced cellular oxidative stress[107]. *In vivo* investigations on Sprague Dawley rats consuming high-fat diet showed that curcumin not only lowered the visceral fat, cholesterol and low-density lipoprotein but also suppressed the Notch-1 protein in liver cells[108]. The photosensitizing potential of curcumin in induction of apoptosis, inhibition of cell proliferation and regulation of Notch signaling has been demonstrated in cervical cancer cell line Me180. The cells incubated for 6 h with 1 μM solution of DAPT {N -[N- (3, 5-difluorobenzene acetyl-l-propionyl)]-(S)-phenylglycine tert-butyl}, which is a Notch receptor blocker and γ-secretase inhibitor in combination with 2.5 μM solution of curcumin were irradiated with laser (445 nm, 100 J/cm^2). After 24 h, the group receiving curcumin and DAPT along with photodynamic treatment (PDT) showed increased apoptotic cell death and a remarkable inhibition rate of 79.27% in Notch1 mRNA expression whereas the group receiving DAPT alone and curcumin-PDT showed 39.99% and 32.33% inhibition rate respectively[109].

CURCUMIN: INROADS INTO *IN VIVO*

The *in vitro* performance of any given compound is important for preliminary progress in drug development, however *in vivo* activity strengthens its claim of bearing the desirable therapeutic potential. Curcumin has been widely explored for its pharmaceutical potential for *in vitro* and *in vivo* investigations with remarkable outcomes. The concerns regarding poor water solubility (0.6 μg/mL) have been addressed through various methods to increase the bioavailability for *in vivo* studies. Successful efforts have been made through preparation of various formulations like nanoparticles[110-113], liposomes[114,115] and combinatorial treatment[116-119] of curcumin with anticancer agents. It is important to note that free curcumin has also shown commendable activity during *in vivo* studies despite its limitations of lower water solubility, stability and bioavailability but the formulated curcumin or curcumin in combinatorial treatment has exceeded the performance of isolated treatment of free curcumin in majority of the cases.

Thus, a formulation overcoming challenges of solution stability, bioavailability, targeted delivery and lowest possible toxicity is much sought after in the case of every drug and curcumin is also not an exception in this regard. Many efforts have been successful in this direction and they have led to appreciable *in vivo* performance. A nano-suspension prepared from d-α-Tocopherol polyethylene glycol 1000 succinate and curcumin increased the water solubility by more than 400 times[120] and the lyophilized nano-suspension, produced fine powder which could be again reconstituted by the addition of water.

The *in vivo* findings are not only important to ascertain the desirable pharmaceutical effect in a more natural environment but also to understand the pharmacodynamics, pharmacokinetics, toxic effects on vital organs like heart; kidney; liver and spleen while providing insights on mechanistic aspects of mode of action of a drug on histological and immunohistochemical examination of tissues. Careful recording of physiological and behavioral changes in the *in vivo* studies, changes in total body weight and survival time are important aspects of pre-clinical studies. The pre-clinical *in vivo* studies are crucial in the case of any molecule to prove its eligibility as a suitable candidate for advanced investigations.

Curcumin against brain cancer *in vivo*

Subcutaneous and intracerebral orthotopic model of Human glioma U-87 cells in athymic mice on intraperitoneal dose of curcumin (120 mg/kg/day) showed less than 50% decrease in median tumor volume in subcutaneous xenograft while in the orthotopic model, the average life span of group receiving similar dose increased by 12% as compared to the control group[121]. In Female SCID mice xenograft model, human primary medulloblastoma cells (DAOY) were subcutaneously injected and after 30 days, the animals were given oral gavage of curcumin (1 mg/kg) dissolved in corn oil[122]. The tumor growth inhibition in curcumin treated group was significantly noticeable as compared to the control group. The

group of Smo/Smo transgenic medulloblastoma mice receiving oral dose of curcumin was reported to have a median survival time of 192 days as compared to the control group, which had a median survival time of 144 days. This observation is in agreement with earlier claims of ability of curcumin to cross Blood Brain Barrier[123,124]. Mechanistic insights in xenografted human medulloblastom D425 cells in athymic mice showed overexpression of p65 subunit of NF-κB and the curcumin treated group showed tumor growth inhibition which can be partially attributed to down regulation of p65 subunit[125].

In another *in vivo* investigation, human glioblastoma U87-MG cells-inoculated nude mice were administered with 100 mg/kg per day of curcumin in DMSO in Phosphate Buffer Saline through intra-tumoral injections. After seven days, significant decrease in tumor size was observed in curcumin treated group. Microscopic examination post Acridine Orange staining showed increased acidic vesicular organelles in curcumin treated cells with intact nuclei, pointing towards curcumin-induced autophagy being responsible for cell deaths[126].

Curcumin against breast cancer *in vivo*

In the xenograft model of triple-negative human breast cancer MDA-MB-231 lines, curcumin showed reduction in tumor weight in a dose dependent manner and the most effective dose was reported as 200 μg/kg of curcumin administered through intraperitoneal injections for 28 days[127]. Transmission electron microscope images showed very distinct morphological changes related to apoptotic cell death without significant side effects on the animals. Oral dose of curcumin in combination with naringenin (20 mg/kg each) received by Swiss albino mice, transplanted with murine mammary Ehrlich ascites carcinoma (EAC) cells, resulted in reduction in the formation of new blood vessels in peritoneal and inner skin linings with reduction (80%) of total number of cells/mL in ascites fluid[128]. Athymic mice xenograft model of human triple-negative breast cancer MDA-MB-231 cells showed significant decrease in angiogenesis, cell proliferation and tumor size on treatment with 300 mg/kg/day intraperitoneal (i.p.) dose of curcumin[129]. Another xenograft model of triple negative breast cancer MBCDF-T cells in nude mice on combinatorial treatment of calcitriol (0.25 μg in 100 μL i.p., once a week) and curcumin (40 mg/kg daily in drinking water) showed inhibition of vascularization and tumor growth[130].

Phosphorylated calixarene (POCA4C6)-encapsulated curcumin on intra-tumoral injection [providing (29.2 mg/kg)] showed strong inhibition of tumor growth in xenografted triple negative Breast cancer cell line BT-549 with indication of substantial early apoptosis as compared to the groups treated with empty micelles and free curcumin. Increased bioavailability through micelle-encapsulated delivery of curcumin was established with the help of increased fluorescence showing increased curcumin-accumulation in tumor[131]. MCF-7 xenograft subcutaneously inoculated in BALB/c nude mice when treated with a combination of paclitaxel and curcumin encapsulated in biodegradable polymeric nanoparticles prepared from tri-block copolymer of poly (ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) showed highest tumor growth inhibition with insignificant loss in total body weight and highest survival percentage as compared to that of control group and groups treated individually with paclitaxel and curcumin[132].

Human Breast cancer BT-474 cells with overexpression of HER-2, xenografted in athymic nude mice showed promising results with decreased mean tumor size as compared to other groups on treatment with 45 mg/kg dose of curcumin twice/week in combination with herceptin (2 mg/kg) once a week on intraperitoneal injection for four weeks[133]. A unique conjugate of curcumin was reported with membrane associated protein, Annexin A2 for the treatment of xenograft model of highly invasive Breast cancer cell line MCF10CA1a, which also showed overexpression of Annexin A2. PLGA nanoparticles loaded with Annexin A2-Curcumin conjugate at a dose of 20 mg/kg every alternate day for 32 days, decreased the tumor volumes by 44% ± 5.2% along with remarkable inhibition of neovascularization[134]. A subcutaneous xenograft model of triple negative breast cancer cell line 4T1 in Female Balb/c mice showed 27% reduction

in the initial size of tumor on treatment with Curcumin loaded nanocompositen (NC) of Fe_3O_4 core and SiO_2 shell on intra-tumoral injection of 40 μL of NC (20 μg curcumin, 0.46 mg/mL) followed by irradiation with a blue diode laser (450 nm, 150 mW/cm2) for 3 minutes and then second irradiation with near infrared laser (808 nm, 0.5 W/cm2) for 7 minutes on every alternate day for two weeks[135]. The observations are significant in this study considering availability of fewer treatment options in the case of triple negative breast cancer.

Curcumin against Cervical Cancer *In Vivo*

Exosomes-extra cellular vesicles - as drug carriers are being considered for *in vivo* administrations. A formulation of curcumin with bovine milk-derived exosomes (Exocur) with a curcumin load of 18%-24% increased the bioavailability in various tissues. Human Cervical cancer (CaSki) xenograft in immunodeficient athymic female nude mice on treatment with 20 mg/Kg of Exocur decreased the tumor volume by 61% while free curcumin showed no effect on tumor size[136]. The same study reported no toxic effect of Exocur on mice on oral administration for two weeks at a dose of 2.5 mg/kg.

Liposomal curcumin (intraperitoneal dose of 25 mg/kg on alternated days) sensitized the human cervical cancer HeLa cell xenograft in non-obese diabetic SCID mice and 3-methylcholanthrene-induced cervical multistage squamous carcinoma in Swiss albino mice to Paclitaxel (intraperitoneal dose of 10 mg/kg, twice in a week) treatment. The combinatorial treatment of curcumin and paclitaxel reduced the tumor incidence by 76 percent as compared to control group whereas groups individually treated with curcumin and paclitaxel showed reduction of 40% and 56% respectively. Mechanistic observations showed that NF-κB activation caused by paclitaxel was suppressed on combinatorial treatment of curcumin and helped in inhibition of tumor growth in xenograft tumors[137].

Curcumin against colorectal cancer *in vivo*

The BALB/c nude mice xenograft model of human colorectal carcinoma cells HCT116, where HCT116 cells were separately transfected with pre-mRNA processing factor 4B (PRP4) and pre-mRNA processing factor 8 (PRP8), on treatment with intraperitoneally-injected 50 mg/kg of curcumin showed that the overexpressed PRP8 could not resist the curcumin-induced apoptosis as evident from tumor size and Western blot analysis showing overexpressed PRP8. PRP4 was hypothesized to resist the curcumin-induced apoptosis due to its kinase domain on the basis of earlier investigations and tumor growth did not get affected, which was also complemented with overexpressed PRP4 shown in western blot analysis. Further confirmations of hypothesis were made after deletion of kinase domain from PRP4, where curcumin successfully regulated tumor size in $P4K^{-/-}$ HCT116 xenograft. These mechanistic insights implicated the role of kinase domain of PRP4 along with apoptosis inducing potential of curcumin[138].

Curcumin bonded to human serum albumin (HSA) nanoparticles not only showed 300 times increased water solubility but also showed 14 times higher accumulation in tumor on intravenous administration after 1 hour as compared to that of free curcumin in the HCT1116 xenograft. 66% tumor growth inhibition by curcumin loaded HSA nanoparticles as compared to 18% tumor growth inhibition by free curcumin can per partially attributed to increased solubility and bioavailability of curcumin due to curcumin-HAS nanoparticle formulation[139]. A remarkable formulation of turmeric with phosphatidylcholine (1:4), which is called Mervia, showed five times increased bioavailability of curcumin as compared to free curcumin. Mervia was granted a US Patent (No. WO2013176555A1) in 2017 and recognized under improved complexes and compositions containing curcumin category. A combinatorial treatment of Mervia mixed with diet and biweekly intraperitoneal injection of oxaliplatin (7.5 mg/kg) in human colorectal cancer HCT116 cells xenograft for three weeks in female nude mice showed highest decrease of 51% in tumor volume[140]. Sub-toxic doses of curcumin (50 mg/kg) in combination with oxaliplatin (25 mg/kg), when administered every alternate day for 22 days in the human LoVo colorectal cells xenograft model in

Table 3. Clinical trials of Curcumin

Group size	Formulation	Health status of volunteers	Dose per day	Average peak serum/ plasma concentration in μM	Remarks	Ref.
12	Powdered extract of curcuminoids in capsule	Healthy	10 g (N = 6) 12 g (N = 6)	No free curcumin was detected in plasma	No adverse side effects	[175]
25	Curcumin powder	Patients with one of the following conditions a) recently resected urinary bladder cancer b) arsenic Bowen's disease of the skin c) uterine cervical intraepithelial neoplasm d) oral leukoplakia e) intestinal metaplasia	4 g 6 g 8 g	Peak serum level (PSL) 0.51 ± 0.11 0.63 ± 0.06 1.77 ± 1.87	No adverse effect and improvement in precancerous lesions	[176]
06	Theracurmin (nanoparticle formulation)	Healthy	150 mg and 210 mg	Peak plasma level (PPL) 0.74 ± 0.18	No adverse effect except for one report of diarrhea in one volunteer after a single oral dose of 150 mg	[177]
16	Theracurmin (nanoparticle formulation) in 100 mL flavored drink	Patients receiving gemcitabine based therapy for pancreatic cancer or biliary tract cancer	200 mg (N = 10) 400 mg (N = 06)	PPL 0.87 1.19	Improvement in adverse effect of chemotherapy	[178]
10	Curcumin in chewing gum	Healthy	2 g	PSL 0.45 ± 0.17	Decreased levels of pro-inflammatory marker TNF-α is observed	[179]
17	Solid-lipid particles loaded with curcumin in capsule	06 Healthy 11 Patients with metastatic osteogenic sarcoma	400 mg to 1.6 g	PPL at dose of 1.6 g 0.11 ± 0.024	No adverse effects	[180]
25	Caplet	Advanced pancreatic cancer already treated through surgery or radiotherapy or chemotherapy	8 g	PPL 0.059 to 0.11	No adverse effect in the participants and one patient showed brief reduction of 73% in tumor volume	[181]

Theracurmin was administered in a group of 16 patients-undergoing gemcitabine-based chemotherapy for pancreatic cancer- in the form of 100 mL flavored drink with an initial dose of 200mg followed by doubling of dose in the absence of adverse side effects. The peak plasma levels was found to be 1.19 μM with a dose of 400 mg/day. The patients receiving Theracurmin showed improvement on adverse effects caused by chemotherapy and improvement in scores of quality-of-life[178].

Healthy volunteers used formulation of curcumin in the form of gum administered over a period of 1h with chewing and keeping the gum for 4 minutes against buccal mucosa. The peak serum concentration was recorded to be 0.45 ± 0.17 μM at 4 h with decreased levels of pro-inflammatory biomarkers TNF-α with ~ 2 g of released curcumin[179].

Eleven patients 7 males and 4 females in the age group of 12-26 years, suffering from advanced stage of metastatic osteogenic sarcoma and 6 healthy volunteers on treatment of solid-lipid particles loaded with curcumin in capsule form showed increased levels of curcumin in plasma and decreased level of TNFα[180]. No adverse effects were noticed in these patients, which could be correlated with curcumin consumption. The plasma levels of curcumin were constantly found to be in the range of 0.11 ± 0.024 μM in patients on treatment with the nanoformulation. In a Phase II clinical trial with 25 patients (median age 65 year) suffering from advanced pancreatic cancer already undergone surgery, radiotherapy or chemotherapy were treated with a daily oral dose of curcumin (8 g) in caplets for 8 weeks[181]. One patient showed a brief reduction of 73% in tumor and no adverse effect in all the patients and the peak plasma level of curcumin remained in the range 0.059 to 0.11 μM for the one month duration. A summary of clinical trials of curcumin has been compiled in Table 3.

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