INTRODUCTION

Curcumin (diferuloylmethane), a polyphenolic phytochemical is the major pigment present in turmeric, a popular spice in Oriental cuisine. Turmeric was used even at the time of Marco Polo as a spice, dye and in therapy [1]. Curcumin is a polyphenolic agent with anti-inflammatory, antioxidant, and anticarcinogenic properties [1-3]. This compound has anti-proliferative and apoptotic activity against different types of cancers, including colon cancer [4], stomach and skin tumors [5], breast cancer [6,7], prostate cancer [8], and head and neck cancer [9]. While different cancer cell lines have varying degree of sensitivity toward curcumin, non-transformed cells are generally less sensitive [10]. Curcumin disrupts different stages of carcinogenesis, including cell proliferation, survival, angiogenesis and metastasis [11]. Curcumin inhibited cell signaling pathways involving Akt, NF-xB, AP-1 and JNK [11,12]. Curcumin also has inhibitory effects on various signaling proteins, including cyclooxygenase, nitric oxide synthase, matrix metalloproteinases and protein kinases [13,14].

We examined the effects of curcumin on Human Epidermal growth factor Receptor-2 (HER-2) over expressing human breast...
cancer cells. HER-2 is the product of the HER-2/neu or ErbB-2 gene that encodes a 185 kDa protein [15,16]. It is overexpressed in 30% of breast cancers and is associated with poor prognosis [17]. HER-2 overexpression is associated with rapid progression through the cell cycle [18]. The progression of cells through different phases of the cell cycle is controlled by a group of functionally related proteins, cyclins, Cyclin Dependent Kinases (Cdk) and their inhibitors [19,20]. Progression through the cell cycle requires activation of cyclin D (D1, D2 and D3)-Cdk4/Cdk 6 and cyclin E-Cdk2 complexes at the G1/S phase, cyclin A-Cdk2 during S phase, cyclin A-Cdk1 during G2, and cyclin B-Cdk1 during the M phase [19]. Curcumin inhibited the proliferation of head and neck cancer cells by arresting the cell cycle in the G2/M phase [19]. Curcumin inhibited the proliferation of head and neck cancer cells, G2/M phase [20,21]. Curcumin has been shown to down-regulate HER-2, whereas it induced growth arrest of MCF-7 breast cancer cells in a density of 5 x 104 cells/well in 24-well plates. Cells were dosed 20 h after plating, with required concentrations of curcumin. Medium was changed and cells re-dosed at 48-hour intervals.

After the appropriate treatment periods, live cells were counted using the trypan blue exclusion method, using a hemocytometer.

Apoptosis assay

SK-BR-3 cells (2x104 cells/100 mm dish) were plated in triplicate in 100 mm dishes. After 24 h, cells were treated with appropriate concentrations of curcumin for 24, 48 and 72 h. At the indicated time point, cells were harvested in PBS, and fixed in 1% paraformaldehyde. After two washes in PBS, cells were resuspended in ethanol and stored at -20°C until further analysis. Percentage apoptosis was determined using the APO-BrdU assay kit from Pharmingen (San Diego, CA, USA). For this assay, the cell pellet was incubated with bromolated deoxyuridine triphosphate (BrdU) and TdT enzyme for 24 h at 22°C. BrdU incorporated into the 3’-hydroxyl termini of double- and single-stranded DNA was identified by staining the cells with a fluorescent labeled anti-BrdU monoclonal antibody using flow cytometry (Coulter Cytomics FC500 Flow Cytometer, Beckman Coulter, Inc. (Fullerton, CA).

Cell cycle analysis

For cell cycle analysis, SK-BR-3 cells (2x104 cells/100 mm dish) were seeded and incubated for 24 h, and then treated with curcumin for 24, 48 and 72 h. Triplicate plates from each treatment group were washed with PBS and covered with a buffer containing 40 mM sodium citrate, 250 mM sucrose and 5% DMSO, and stored at ~70°C. On the day of DNA analysis, cells were thawed, and the citrate buffer was removed. Cells were trypsinized for 10 min and then treated with a solution containing a trypsin inhibitor and RNase for 10 minutes. Cells were stained by adding propidium iodide solution in sodium citrate buffer and analyzed by a Coulter flow cytometer and cell distribution calculated with cytologic software [25].

qRT-PCR

Cells were plated and treated with curcumin, as described in Apoptosis Assay above. At the end of the treatment time periods, media was removed and cells treated with Trizol reagent. RNA was isolated using Trizol reagent (Invitrogen) and 2 µg RNA was reverse-transcribed using the first strand cDNA synthesis kit (Fermentas, Inc., Glen Burnie, MD) with random hexamers as primers. The expression of Her2, p21, p27, Ccnb1, Ccnd1, Ccna and Gapdh genes was determined by real-time PCR using the SYBR Green PCR Master Mix (Bio-Rad) with the following primers: 5’-CAAGCGCCTCACAGAGATC-3’ and 5’-TTACACTCATGGAGGAGCAG-3’ for Her2 (173 bp); 5’-GGATCCTCTGTGACTACTCC-3’ and 5’-GGATGAGTGGGATGAACAGGAC-3’ for Ccnb1 (200 bp); 5’-ATCTACACGGAACATCTATC-3’ and 5’-AAGGGGCAAGCAAGG-3’ for Ccnd1 (193 bp); and 5’-AGCTGACTGTCGTCCTCC-3’ and 5’-AAGGAGTGGATGAAGGAGGAG-3’ for Ccna (192 bp); 5’-TGGTTGATACCTGCCTCC-3’ and 5’-AAGGAGTGGATGAAGGAGGAG-3’ for Ccnd1 (193 bp); 5’-GGATGAGTGGGATGAACAGGAC-3’ for Ccnb1 (200 bp); 5’-CATGAGGAATGACAGACTATC-3’ and 5’-CAAGAGGCAAGAGAGG-3’ for Gapdh (113 bp). A total volume of 25 µL was used for qPCR in an IQ5™ thermocycler (Bio-Rad). Amplification conditions were 95°C for
3 min, then 40 cycles of 95 °C for 15 s, and annealing for 30 s at 60°C. qPCR products were normalized relative to that of Gapdh to correct for template input variation. Data is presented as fold differences in expression of the indicated gene relative to Gapdh. Standard curve was produced for every target using six 4-fold serial dilution.

Western blots

Cells (2.5 x 10^6/100 mm dish) were washed twice with ice-cold PBS and lysed with the addition of ice-cold lysis buffer [150 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1% Nonidet P-40, 2 mM EDTA, 50 mM sodium fluoride, 0.2% SDS, 1 mM sodium vanadate, and 1 X concentration of a protease inhibitor cocktail (Calbiochem, San Diego, CA)]. Thirty micrograms of protein (determined by the Bradford protein assay) was diluted in 2X SDS-PAGE Laemmli buffer [150 mM Tris-HCl (pH 6.8), 1% Nonidet milk, 4% SDS, 7.5 mM DTT, 0.01% bromophenol blue] and separated on a 7.5, 10 or 12% SDS-polyacrylamide gel. Proteins were transferred to PVDF membrane. After blocking with 5% nonfat milk, membrane was immunoblotted with an appropriate dilution of the primary antibody. Protein bands were visualized using horseradish peroxidase–conjugated secondary antibody and a chemiluminescence based detection system. As a control, membranes were stripped and rebotted with anti-β-actin monoclonal antibody, and blots developed using Kodak XAR Biomax film.

Statistics

All experiments were repeated at least three times. Statistical difference between control and treatment groups was determined by one-way ANOVA followed by Dunnet’s post-test (GraphPad Prism Software program, San Diego, CA). P < 0.05 was considered to be statistically significant. Gel bands were quantified using the ImageJ software (NIH) [26].

RESULTS

Effect of Curcumin on cell proliferation and apoptosis

We first studied the effect of different concentrations of curcumin on HER-2 over expressing SK-BR-3 cells by the trypan blue exclusion method. We treated SK-BR-3 cells with vehicle alone (DMSO) or 1, 2.5, 5, or 10 µM curcumin for 24 h. Only live cells not able to uptake trypan blue were counted. DMSO treatment resulted in <5% change in cell number. Figure 1A shows results of the cell proliferation assay. We observed a dose-dependent decrease in cell number with increasing concentrations of curcumin, with an IC_{50} of 3.0 ± 0.5 µM at 24 h of treatment. Similar cytotoxicity was observed at 48 and 72 h of treatment, except that viable cells were eliminated at lower concentrations, with <10% cells remaining at 72 h at 10 µM concentration. These results indicate that curcumin can induce growth inhibitory and cell killing effects in HER-2 over expressing SK-BR-3 cells in a concentration-dependent manner.

In the next set of experiments, we quantified the effect of curcumin on apoptosis of SK-BR-3 cells for 24, 48 and 72 h using the APO-BrdU assay kit. Experiments were conducted three separate times and mean ± SD are shown. Apoptosis was determined by APO-BrdU assay kit. Experiments were conducted three separate times and mean ± SD are shown (* P < 0.05; # P < 0.001).

Figure 1 A) Effect of curcumin on viability of SK-BR-3 cells. SK-BR-3 cells were treated with different concentrations of curcumin for 24, 48 and 72h. At these time-points, cells were counted by trypan blue exclusion using a hemocytometer. Experiments were conducted three separate times and mean ± SD are shown. B) Effect of curcumin on apoptosis of SK-BR-3 cells. Cells were treated with different concentrations of curcumin for 24, 48 and 72h. Apoptosis was determined by APO-BrdU assay kit. Experiments were conducted three separate times and mean ± SD are shown (* P < 0.05; # P < 0.001).

Effect of curcumin on cell cycle of SK-BR-3 cells

We next determined the effect of curcumin on the distribution of cells in different phases of cell cycle by curcumin treatment. Cells were treated with DMSO or 5, 10, 25 and 50 µM curcumin for 24 h. As shown in Table 1, we observed distinct effects on cell cycle depending on the concentration of curcumin. At 10 µM of double- and single-stranded DNA. After incorporation, these sites were identified by flow cytometry by staining the cells with a fluorescein-labeled anti-BrdU monoclonal antibody. Figure 1B shows the effect of curcumin on apoptosis of SK-BR-3 cells. Percentage of apoptosis (± SD) in cells treated with 5 and 10 µM curcumin for 24 h were 5.0 ± 0.71% and 12.0 ± 1.5%, respectively. However, there was a remarkable increase in apoptosis when cells were treated with 25 µM (79.6 ± 1.3%) or 50 µM (87.8 ± 1.9%) curcumin. In vehicle treated cells, apoptosis was 2.28 ± 0.04%. Apoptotic cells remained in the range of 7 to 12% after 72 h of treatment with 10 µM curcumin.

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concentration, curcumin caused the cells to accumulate in the G_2/M phase. However, cells appeared to be evenly distributed between G_1, S and M phases 24 h of treatment with 25 and 50 μM curcumin.

**Effect of curcumin on mRNA levels of critical cell signaling and cell cycle regulatory genes**

SK-BR-3 cells are critically dependent on the over expression of HER-2 protein and the subsequent up-regulation of cell signaling pathways. We therefore examined the expression of HER-2 gene in response to curcumin treatment using real-time qPCR analysis. We also determined mRNA levels of cell cycle regulatory proteins such as cyclins and cyclin dependent kinase inhibitors. As shown in Figure 2, HER2 mRNA levels were reduced by 65 to 70% at 10 to 50 μM curcumin treatment for 16 h to 24 h. However, cyclin dependent kinase inhibitors that are typically induced by growth inhibitory and apoptotic agents showed differential effects at different concentrations. There was a remarkable 5-fold increase in p21 mRNA in samples treated with 10 μM curcumin, for 16 h, but there was a 50% decrease from the highest level at 25 and 50 μM concentrations. At the 24 h time point, p21 remained 2.5-fold at higher than the control at all concentrations of curcumin. The p27Kip1 mRNA showed a less remarkable effect of about 30% increase in cells treated with 10 μM curcumin and a decrease from the maximum at higher curcumin concentrations. There was a 30 to 40% decrease of p27 mRNA level compared to the control in cells treated with 50 μM curcumin for 16 or 24 h.

Cyclin A and cyclin B1 are generally induced in the S and G_2/M phases of cell cycle whereas cyclin D1 and cyclin E are induced in the G_1 phase. Interestingly, curcumin was not able to alter cyclin A (Ccna) and cyclin B1 (Ccnb1) mRNA levels at 10 μM

### Table 1: Effect of Curcumin on Cell Cycle Distribution of SK-BR-3 Cells.

<table>
<thead>
<tr>
<th>Curcumin Conc., μM</th>
<th>G_1</th>
<th>S</th>
<th>G_2/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56.05 ± 2.3</td>
<td>20.82 ± 1.6</td>
<td>23.17 ± 0.5</td>
</tr>
<tr>
<td>5</td>
<td>59.38 ± 0.9*</td>
<td>17.65 ± 0.8</td>
<td>22.76 ± 1.2</td>
</tr>
<tr>
<td>10</td>
<td>24.82 1.1'</td>
<td>20.07 ± 0.6</td>
<td>56.14 ± 1.1*</td>
</tr>
<tr>
<td>25</td>
<td>32.69 ± 0.8'</td>
<td>31.47 ± 3.5'</td>
<td>36.77 ± 3.9'</td>
</tr>
<tr>
<td>50</td>
<td>33.24 ± 1.6'</td>
<td>28.98 ± 2.0'</td>
<td>38.49 ± 3.0'</td>
</tr>
</tbody>
</table>

SK-BR-3 cells (2x10^6) were treated with curcumin for 24 h. Cells were stained by adding propidium iodide solution in sodium citrate buffer and analyzed by a Coulter flow cytometer. Floating cells were not collected. Percentage distribution of cells in different phases of cell cycle was calculated with cytologic software. Data are the mean ± SD of three separate experiments and the p values were determined by ANOVA followed by Dunnet's post-test comparing curcumin treated groups with control group (* P < 0.01; # P < 0.05).

![Figure 2](image_url) Effects of curcumin on the expression of HER-2 and other mRNAs by qRT-PCR. Cells were treated with different concentrations of curcumin for 16 and 14 h. HER-2, p21, p27, cyclin A, Cyclin B1, cyclin D1 and Cyclin E mRNAs were quantified.
concentration, but at higher concentrations, there was a 50 to 60% decrease in the mRNA levels of these genes, both at 16 and 24 h of treatment. Cyclin D1 (Ccnd1) and cyclin E (Ccne) showed 50 to 75% decrease after treatment with 10 to 50 µM curcumin, both at 16 and 24 h of treatment.

**Effect of curcumin on HER-2 protein levels**

Considering the critical role of HER-2 protein in the regulation of SK-BR-3 cells, we next examined the effect of curcumin on HER-2 protein levels. Since HER-2 kinase activity is regulated by its phosphorylation status, we determined the levels of total HER-2 and p-HER-2 proteins by Western immunoblots. To examine the potential of early changes in phosphorylation status, SK-BR-3 cells were treated with curcumin for 4, 8, 16 and 24 h. Proteins from cell lysates were then analyzed by Western blotting and probed for p-HER-2, total-HER-2 and β-actin (Figure 3A). Relative band intensities with reference to those of β-actin are presented in Figures 3B. We found that curcumin caused a time- and dose-dependent reduction in both p-HER-2 and total-HER-2 levels. Furthermore, 25 and 50 µM curcumin concentrations significantly reduced p-HER-2 levels by 4 h. By 24 h, both p-HER-2 and total-HER-2 levels were reduced by 80 to 90% in cells treated with 25 and 50 µM curcumin.

**Effect of Glutathione pre-treatment of SKBR-3 cells on curcumin induced cell death/growth inhibition**

In order to understand the mechanism of action of curcumin on SK-BR-3 cells, we examined the role of the ROS pathway since curcumin has been reported to generate ROS as a precursor to inducing cell death. SK-BR-3 cells were pre-treated with 5 mM glutathione according to the protocol of Syng-Ai et al. [27] for 1 h before treatment with curcumin. Cells were then harvested at the end of 24 h and viable cells counted using a hemocytometer. Results are presented in Figure 4. We found that pre-treatment with glutathione significantly attenuated the growth inhibition induced by curcumin in SK-BR-3 cells. Glutathione (5 mM) exerted protective effect on the cytotoxicity of curcumin at 5 to 50 µM concentrations. Cells treated with 50 µM curcumin resulted in 90% reduction in viable cell number, however, pre-treatment with glutathione resulted in only ~60% reduction of cell number.

Since glutathione pre-treatment rescued SK-BR-3 cells from cell death, we next examined the effect of glutathione on HER-2 protein levels (Figure 5). SK-BR-3 cells were treated with 0, 5, 10, 25 and 50 µM curcumin for 24 h after pre-treatment with glutathione. Cells were harvested and cell lysates subjected to Western blotting. Cells treated with 25 to 50 µM curcumin plus 5 mM glutathione showed a 2-fold induction of total-HER-2 protein levels compared to samples treated with curcumin alone. However, HER-2 protein levels were still lower than that of the control group. These results showed that glutathione was capable to partially restoring total-HER-2 level.

**DISCUSSION**

Our results indicate that curcumin is capable of inhibiting...
the growth of HER-2-positive SK-BR-3 cells. Curcumin caused cell growth inhibition with an IC\textsubscript{50} of 3.0 µM, although apoptosis was not significant at <5 µM concentrations. In contrast, majority of cells (>80%) underwent 25 and 50 µM concentrations. At 10 µM concentration, curcumin induced G\textsubscript{2}/M arrest, although, at higher concentration, cells were evenly distributed in G\textsubscript{1}, S, and G\textsubscript{2}/M phases. Real-time qPCR analysis showed that HER-2 mRNA level was reduced by 65 to 70% at 10 to 50 µM curcumin. Significant decreases in HER-2 protein and p-HER-2 levels were also observed after curcumin treatment. Pre-treatment with glutathione partially reversed the growth inhibition induced by curcumin and restored HER-2 protein levels.

Curcumin is known to induce apoptotic activity against a variety of cancers, including, stomach and skin tumors as well as breast and prostate cancer cells [3,5,6,11]. However, induction of apoptosis depends on curcumin concentration, cell type, and environmental factors [28]. Cells treated with 25 and 50 µM curcumin showed a remarkable reduction in cell viability and increase in apoptosis at the 24 h time point. It has been reported that curcumin can cause cell growth inhibition without inducing apoptosis in leukemia cells [28], a finding similar to our results of lack of apoptosis at <5 µM curcumin. In some breast cancer cell lines, curcumin-induced cell killing has been reported to differ from classical apoptosis [29].

Inhibition of cell growth was also associated with a decrease in p-HER-2 as well as total-HER-2 protein levels. Curcumin has been shown to deplete and accelerate the degradation of HER-2 protein by causing its dissociation from the molecular chaperone, GPR94 [3]. These results are consistent with other studies that have shown an inhibition of HER-2 signaling by Herceptin or the down-regulation of erbB2/neu promoter activity as a mechanism of cell growth inhibition in HER-2 over expressing tumor cells [29,30].

We observed that curcumin in treatment of SK-BR-3 cells caused cells to arrest in the G\textsubscript{2}/M phase at 10 µM curcumin concentration. In addition, p21 was also induced at this concentration. The low level of apoptosis at 10 µM curcumin might stem from the observation that for efficient apoptosis, cells must escape G\textsubscript{2} arrest which is an initial response to DNA damage [31]. At 24 h, cells treated with 25 and 50 µM curcumin showed an induction of p27 mRNA and increased accumulation of S phase cells. Similar to the effects seen herein, dasatanib, a tyrosine kinase inhibitor represses growth of head and neck cancers and lung cancers by inducing p27 and affecting the G\textsubscript{1}/S phase transition of the cells [32].

We also examined whether the effect of curcumin is related to its role as a modulator of the redox state of the cell. While curcumin is reported to induce apoptosis by depletion of glutathione and generation of ROS in breast cancer cells [33], it is also a potent scavenger of a variety of ROS [34]. Curcumin can act as pro-oxidant in the presence of metals ions like copper in the environment or at high concentrations in vitro [35]. At 10 µM concentration, curcumin acts as an anti-oxidant; however, at 50 µM it generates superoxide radicals and acts as a pro-oxidant [23,24]. Oxidative stress signals induced by the formation of ROS and glutathione depletion are considered as important activators of apoptosis [35]. We observed that pre-treatment of cells with 5 mM glutathione reduced growth inhibitory effects of curcumin and partially restored HER-2 protein levels.

The mechanism by which ROS modulates HER-2 protein levels is not known although it can be speculated that cysteine thiol modification is involved. Within the acidic intracellular

![Figure 4](image_url)

**Figure 4** Effect of glutathione pre-treatment of SK BR-3 cells on curcumin-induced growth inhibition and death. Cells were treated with 5 mM glutathione for 1 h before addition of curcumin. Cells were harvested after 24 h and counted using the trypan blue exclusion assay. Results shown are the mean ± SD from three experiments (* P <0.01, comparing control with treatment groups; # P <0.01, comparing curcumin treated group with its respective curcumin + glutathione treated group.)
environment of cells, curcumin exists in the bis-keto form which is a potent H-atom donor [36]. As a result, curcumin can also directly interact and modify thiols groups present on cysteine groups on proteins like NF-B and AP-1 and modulate their transcriptional activity [37]. HER-2 protein has two cysteine rich extracellular subdomains that are thought to play an important role in ligand-dependent transactivation [38]. Therefore, it is possible that curcumin modifies HER-2 and hastens its degradation or turnover rate. One of its other targets includes thioredoxin reductase, an enzyme involved in combating oxidative stress by maintaining reduced thioredoxin [39]. Lack of reduced thioredoxin can lead to S-phase arrest as it is involved in DNA synthesis through its interaction with ribonucleotide reductase [39]. Apoptosis induction through ROS may be only part of the cell death mechanism since glutathione supplementation resulted in only partial restoration of number of viable cells. Alternatively, ROS may cause irreversible damage to other growth factor signaling pathways important for cell growth.

In conclusion, we demonstrate that curcumin causes potent cell growth inhibition in SK-BR-3 cell lines, a HER-2 over expressing human breast cancer cell line. Curcumin caused G2/M arrest at 10 µM concentration and a high levels of apoptosis at 25 and 50 µM concentrations. Curcumin also caused a decrease in total HER-2 and p-HER-2 and alterations in the expression different cell cycle regulatory genes. Generation of ROS might contribute to curcumin’s anti-proliferative action. Thus, growth inhibitory effects of curcumin in SK-BR-3 cells can be attributed to pleiotropic effects of curcumin on redox-regulated growth signaling pathways. Since antiproliferative effects can be restored by exogenous glutathione, cellular redox status is an important factor in curcumin sensitivity of breast cancer cells.

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