Effects of Capsaicin and Its Analogs on the Growth of Gastric Cancer Cells and Their Structure-activity Relationships In Vitro

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Capsaicin is an organic compound in chili peppers which are consumed by over one quarter of the world’s population daily. Studies have shown that capsaicin can prohibit proliferation in some cancer cells. In the present study, both gastric cancer and normal epithelial cell lines were employed and treated with capsaicin and its analogs and examined for the structure-activity relationship as well. 3-(4, 5-di-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide yellow tetrazole (MTT) assay results showed the order of effectiveness of capsaicin analogs in the used cell culture system was as follows: dihydrocapsaicin > capsaicin > 6-gingerol > vanillin ≥ vanillylamine, and, reactive oxygen species (ROS) and malondialdehyde (MDA) contents were markedly increased; the biological activity pathway of Superoxide dismutase (SOD) and Glutathione Peroxidase (GSH-Px) was up-regulated, whereas, the catalase (CAT) activity was down-regulated by dihydrocapsaicin, capsaicin and 6-gingerol. In conclusion, the results implied that B and C region are indispensable for the anti-cancer activity of capsaicin and CAT activity down-regulation was responsible for apoptosis of gastric cancer cells induced by capsaicin and its analogs.

Keywords: gastric cancer, capsaicin analogs, structure-activity relationship, oxidative stress

Introduction

Gastric cancer is a life-threatening, serious disease to humans and it is the second most prevalent cause of malignant tumor-related death in the world. The highest incidence was found in northeast Asia where Japan, Korea, and China located in (Hartgrink, 2009; Jemal et al., 2008). Right now, there is no any breakthrough in effective treatment; the surgery is the last optional treatment of patients but it mostly works out only in earlier stage of tumor growth and development. Consequently, in recent decades, looking for new drugs for gastric cancer treatment has been gaining more considerable research focus in many laboratories worldwide. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a unique alkaloid found primarily in the fruit of the Capsicum genus and is what provides its spicy flavor (Cordell et al., 1993; Suzuki et al., 1994). It is a crystalline, lipophilic, colorless and odorless alkaloid with the molecular formula C₁₈H₂₇NO₃, molecular weight 305.40 g/mol. The anticancer role of capsaicin has been reported for a long time (Surh, 2002). Capsaicin displayed the antitumor activity not only in “in vitro” experiments but also in “in vivo” studies. The anticancer and chemo preventive effects of capsaicin are closely related to their ability to prevent cell proliferation and migration and to induce cell apoptosis (Luo et al., 2011). Several recent studies demonstrated that capsaicin has antiproliferative effect in hepatic (Jung et al., 2001), gastric (Lo et al., 2005), prostate (Mori et al., 2006), colon (Kim et al., 2004) and leukemic cells (Ito et al., 2004).

Several human chronic disease states, including cancer, have been associated with oxidative stress produced through either increased free radicals and/or a decreased antioxidant level in the target cell and tissues (Klaunig et al., 1998). Many reports found that inducing apoptosis and increasing the oxidative stress were important mechanism for nature products inhibiting the growth of cancer cells (Ji et al., 2011; Kerr et al., 1972). Wang et al. (2011) found that capsaicin induced apoptosis of gastric cancer cells and exerted inhibiting effects on tumor-associated NADH oxidase (tNOX) expression. They considered that forced tNOX down-regulation re-
stored capsaicin-induced growth inhibition in gastric cancer cells. Capsaicin and dihydrocapsaicin induced autophagy but they did not induce apoptosis in HCT116 and MCF-7 cells; on the other hand, capsaicin induced apoptosis in SNU-1 gastric cancer cells (Oh et al., 2008); these results showed that cytotoxic mechanisms were different between cell lines. In the present study, we try to investigate effects of capsaicin on the ROS generation, concentrations of malondialdehyde (MDA), activity of antioxidant enzymes Glutathione peroxidase (GSH-Px), Superoxide dismutase (SOD) and Catalase (CAT) in gastric cancer cells, which might be more significant to elucidating the relationship between oxidative stress and capsaicin-induced apoptosis.

The structure of capsaicin can be divided into A region, a specific aromatic ring configuration; B region, amino acid residues, a hydrogen bond-donating group; C region, a hydrophobic hydrocarbon tail (Fig. 1).

Recently, the structure-activity relationships of capsaicin and its structural modification of capsaicin have received more intensive studies in the research fields. Gerardo et al. (2010) as an example successfully synthesized a series of 14 analogues of capsaicinoids with different linear chain lengths in C location, from 2 to 16 carbon atoms. The result was discovered the lipophilic properties of the synthesized compounds were correlated directly to bioactive metabolism. Karen et al. (2011) also illustrated the relationship between chemical variants of the capsaicin analog and TRPV1 receptor binding as well as cell death. They reported modification of the 3-methoxy-4-Hydro-xy-l-benzylamide vanilloid ring pharma-cophore of capsaicin in A region reduced the potency of the analogs and rendered several analogs being mildly inhibitory. Up to date, there is no any report to make a clear confirmation which the effective region acts a role in cancer fighter.

We selected some capsaicin analogs include two capsaicin derivatives (Dihydrocapsaicin and 6-Gingerol) and two capsaicin metabolites (vanillin and vanillylamine) for the test. 6-Gingerol is deemed of prime importance for the pharmacological activities of ginger, such as antioxidant, anticancer, antimicrobial, and anti-inflammatory properties (Morera et al., 2012). Vanillylamine is the product of capsaicin when it was hydrolyzed at the acid-amide bond. Oxidative deamination of the resulting vanillylamine produces the aromatic aldehyde vanillin (Young and Sang, 1995). In this paper, we will work to further investigate the structural activity relationship of capsaicin and its effects of capsaicin and its analogs (Fig. 2) on the growth of gastric cancer cells (SGC-7901 cells) in order to map the active role region of capsaicin hindering the growth of gastric cancer cells.

Materials and Methods

Materials Capsaicin (98%), Dihydrocapsaicin (98%) and 6-Gingerol (98%) were purchased from National Institute for the Control of Pharmaceutical and Biological Products; vanillin (98%) and vanillylamine (98%) were bought from Sinopharm Chemical Regent Co., Ltd; FC500MCL
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flow cytometer (BECKMAN ltd, USA).

**Cell line and culture** SGC-7901 human gastric cancer cells and GES-1 normal human gastric mucosa epithelial cells were maintained in RPMI 1640 medium supplemented with heat-inactivated 10% fetal bovine serum, 50μg/mL penicillin, and 50μg/mL streptomycin at 37°C in a ratio of 5% CO₂/95% air-humidified incubator. When required, cells were seeded on plates and exposed to chemicals after culturing overnight.

Cell viability assay (MTT staining) Cell viability was assessed by the 3′-(4, 5-dimethylthiazol-2-yl)-2, 5-Diphenyl -tetrazolium bromide (MTT) assay based on the reduction of an MTT into formazan dye by active mitochondria (Mosmann et al., 1983). Briefly, the cells were grown in 96-well plates at a density of 1 × 10⁵ cells/mL for 24 h. After that, cells were exposed to culture medium with capsaicin analogs. After 24 h inoculation, 20 μL of MTT solution (5 mg MTT/mL in PBS) was added to each well of the plate and was continually incubated for 4 h. After washing, the formazan dye precipitations, the amount of which is proportional to the number of living cells, were dissolved in 200 μL of DMSO. The absorbance was read at wavelength 540 nm using a microtiter plate reader. The inhibition rate of cell growth was calculated by the following formula: mean value of treated group/control group × 100%. Triplicate wells were analyzed per each experiment.

**Annexin V binding apoptosis assay** The apoptotic rate of cells was detected using flow cytometry (FCM) with the Annexin V-FITC/PI double labeling method (Brumatti et al., 2008). Translocation of phosphatidylserine (PS) to the outer leaflet of the cellular membrane seems to be a key step in the early stages of apoptosis. Basically, Annexin V, which has a strong affinity for PS, is conjugated to FITC; therefore, it is possible to identify and quantitate apoptotic cells on a single-cell basis by FCM. Theoretically, early and late apoptotic cells and necrotic cells having permeable membranes will bind to Annexin V-FITC. Thereby, PI could be employed to distinguish between viable, early apoptotic and necrotic, late apoptotic cells. PI is excluded by viable cells (FITC-negative) and early apoptotic cells (FITC-positive). Late apoptotic and necrotic cells were stained with both Annexin V-FITC and PI.

In brief, cells in logarithmic growth phase (1 × 10⁵ cells/mL) were plated at 2 mL/well in 6-well plates and allowed to attach overnight. After 24 h, drug was added to the wells in a volume of 2 mL per well. An equal volume of medium was added to the wells in control group. The dishes were incubated for 24 h. Then, cells were harvested, cell suspension was freezing and thawing destroyed and then centrifugation at 14000 rpm for 15 min. The cell pellet was resuspended in 1 mL of fresh incubation medium containing 2′, 7′-dichlorodihydrofluorescin (DCFH) and incubated for 10 min at 37°C. The fluorescence intensity of the 2′, 7′-dichlorofluorescein formed was monitored at 500 nm excitation and 520 nm emission wavelengths. The results were expressed as fluorescent intensity per 10⁵ cells.

**Determination of MDA concentration and enzyme activities of SOD, GSH-Px and CAT in cultured cells** As described above, cells in logarithmic growth phase (1 × 10⁵ cells/mL) were plated at 2 mL/well in 6-well plates and allowed to attach overnight. After 24 h, drug was added to the wells in a volume of 2 mL per well. An equal volume of medium was added to the wells in control group. The dishes were incubated in 5% CO₂ at 37°C for 24 h. Then, cells were harvested, cell suspension was freezing and thawing destroyed and then centrifugation at 14000 rpm for 15 min. However, the supernatant was kept for the determination. Concentration of MDA was determined by the method of Ohkawa et al. (1979), activities of SOD were measured by method of Marklund and Marklund (1974), CAT activity was assayed by the method of Sinha (1974), and GSH-Px activity was determined by the method of Rotruck et al. (1973).

**Statistical analysis** The experimental data was expressed as mean ± S.D. The data was analyzed by the Dunnett test. The differences were considered to be statistically significant when p < 0.05.

**Results**

**Effects of capsaicin and its analogs on the growth of SGC-7901 and GES-1 cells** The effects of capsaicin, dihydrocapsaicin, 6-gingerol, vanillin, and vanillylamine on
The growth of GES-1 and SGC-7901 cells were examined by MTT assay, in which, Dihydrocapsaicin and 6-gingerol are capsaicin analogs; vanillin and vanillylamine are capsaicin metabolites. SGC-7901 and GES-1 cells were administered with 10 to 40 μg/mL capsaicin and its analogs for 6 to 48 h, and the results showed that viability of SGC-7901 and GES-1 cells was inhibited in a time and dose-dependent manner (Table 1). Meantime, SGC-7901 cells are more susceptible to capsaicin and its analogs than GES-1 cells. As indicated, GES-1 cells and SGC-7901 cells treated with 10 μg/mL capsaicin for 6 h were showed the cell viability of 81.6% and 74.5% respectively. The order of effectiveness of capsaicin analogs and its metabolites for suppressing GES-1 cell and SGC-7901 cell proliferation were dihydrocapsaicin > capsaicin > 6-gingerol > vanillin ≥ vanillylamine. It inferred that the capsaicin metabolites (vanillin and vanillylamine) were not the main reason for the anti-proliferation activity of capsaicin; therefore, they will not be utilized for the further experiments.

Effects of capsaicin and its analogs on the apoptosis of GES-1 and SGC-7901 cells In this paper, rates of apoptosis and necrotic cells of GES-1 and SGC-7901 cells treated with 10 μg/mL capsaicin and its analogs were investigated by FCM at 24 h after double staining with Annexin V-FITC and PI. The results showed that capsaicin, dihydrocapsaicin and 6-gingerol could induce apoptosis in GES-1 and SGC-7901 cells. For GES-1 and SGC-7901 cells, the apoptosis index was 22.15%, 21.6%, 18.85% and 21.52%, 26.97%, 21.12% respectively (Fig. 3), there is not the significant difference between GES-1 cells and SGC-7901 cells in apoptosis index. The effectiveness of capsaicin analogs for inducing GES-1 cells and SGC-7901 cells apoptosis were obviously illustrated as dihydrocapsaicin > 6-gingerol > capsaicin respectively.

Effect of capsaicin and its analogs on the generation of ROS in GES-1 and SGC-7901 cells Several studies have implicated ROS generation as a possible mechanism for induction of apoptosis by various anticancer agents (Ito et al., 2004; Singh et al., 2005). We, therefore, try to find whether capsaicin and its analogs induced apoptosis by accelerating generation of ROS in our model. Here, intracellular ROS generation in GES-1 and SGC-7901 cells treated with capsaicin and its analogs was evaluated by fluorescence spectrophotometer. As shown in Fig. 4, concentrations of superoxide radical in GES-1 and SGC-7901 cells treated with capsaicin and its analogs were illustrated in Table 1.

### Table 1. Effects of capsaicin analogs on the viabilities of GES-1 cells and SGC-7901 cells.

<table>
<thead>
<tr>
<th></th>
<th>Capsaicin</th>
<th>Dihydrocapsaicin</th>
<th>6-Gingerol</th>
<th>Vanillin</th>
<th>Vanillylamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cell viability (% of control)</td>
<td></td>
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<td></td>
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<tr>
<td>6 h</td>
<td>10 μg/mL</td>
<td>81.6 ± 3.2c</td>
<td>77.1 ± 3.6c</td>
<td>87.7 ± 1.5b</td>
<td>92.9 ± 2.1ab</td>
</tr>
<tr>
<td></td>
<td>20 μg/mL</td>
<td>60.7 ± 3.6c</td>
<td>56.7 ± 4.2d</td>
<td>74.2 ± 3.2b</td>
<td>83.4 ± 2.8a</td>
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<tr>
<td></td>
<td>40 μg/mL</td>
<td>43.2 ± 2.9d</td>
<td>37.8 ± 4.1e</td>
<td>60.2 ± 2.7c</td>
<td>81.5 ± 2.5b</td>
</tr>
<tr>
<td>24 h</td>
<td>10 μg/mL</td>
<td>76.8 ± 1.8c</td>
<td>72.7 ± 4.5c</td>
<td>81.3 ± 3.0b</td>
<td>90.8 ± 1.5a</td>
</tr>
<tr>
<td></td>
<td>20 μg/mL</td>
<td>55.7 ± 2.7d</td>
<td>53.1 ± 2.8d</td>
<td>67.1 ± 4.1c</td>
<td>81.1 ± 1.9b</td>
</tr>
<tr>
<td></td>
<td>40 μg/mL</td>
<td>30.5 ± 3.4d</td>
<td>25.8 ± 3.4e</td>
<td>51.8 ± 3.2c</td>
<td>78.3 ± 2.5b</td>
</tr>
<tr>
<td>48 h</td>
<td>10 μg/mL</td>
<td>71.5 ± 3.9d</td>
<td>69.3 ± 4.2d</td>
<td>76.7 ± 3.9c</td>
<td>85.8 ± 0.9b</td>
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<tr>
<td></td>
<td>20 μg/mL</td>
<td>50.2 ± 2.8d</td>
<td>45.9 ± 3.7e</td>
<td>60.7 ± 2.1c</td>
<td>74.2 ± 2.0b</td>
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<tr>
<td></td>
<td>40 μg/mL</td>
<td>27.3 ± 3.1d</td>
<td>20.2 ± 4.0e</td>
<td>41.1 ± 3.4c</td>
<td>68.5 ± 1.4b</td>
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<td>B</td>
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<td>Cell viability (% of control)</td>
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<tr>
<td>6 h</td>
<td>10 μg/mL</td>
<td>74.5 ± 3.5c</td>
<td>66.4 ± 3.7d</td>
<td>84.6 ± 1.7b</td>
<td>90.6 ± 2.1a</td>
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<tr>
<td></td>
<td>20 μg/mL</td>
<td>50.7 ± 2.9d</td>
<td>45.4 ± 3.2e</td>
<td>67.1 ± 2.5c</td>
<td>81.5 ± 3.4b</td>
</tr>
<tr>
<td></td>
<td>40 μg/mL</td>
<td>32.6 ± 2.8d</td>
<td>29.2 ± 2.4d</td>
<td>52.9 ± 1.9c</td>
<td>74.4 ± 3.2b</td>
</tr>
<tr>
<td>24 h</td>
<td>10 μg/mL</td>
<td>66.5 ± 4.1d</td>
<td>63.9 ± 4.3d</td>
<td>77.3 ± 2.1b</td>
<td>89.0 ± 1.8ab</td>
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<tr>
<td></td>
<td>20 μg/mL</td>
<td>34.2 ± 2.2d</td>
<td>30.2 ± 2.8e</td>
<td>58.4 ± 2.9c</td>
<td>78.6 ± 2.1b</td>
</tr>
<tr>
<td></td>
<td>40 μg/mL</td>
<td>12.6 ± 3.9d</td>
<td>9.9 ± 3.2e</td>
<td>38.3 ± 2.8c</td>
<td>70.6 ± 2.5b</td>
</tr>
<tr>
<td>48 h</td>
<td>10 μg/mL</td>
<td>62.9 ± 3.8d</td>
<td>61.3 ± 4.2d</td>
<td>67.7 ± 3.4c</td>
<td>83.3 ± 1.9b</td>
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<tr>
<td></td>
<td>20 μg/mL</td>
<td>31.1 ± 3.4d</td>
<td>25.4 ± 3.1e</td>
<td>53.0 ± 2.8c</td>
<td>76.3 ± 2.7b</td>
</tr>
<tr>
<td></td>
<td>40 μg/mL</td>
<td>18.9 ± 2.6d</td>
<td>16.4 ± 2.5d</td>
<td>32.1 ± 2.8c</td>
<td>64.1 ± 2.6b</td>
</tr>
</tbody>
</table>

A: GES-1 cells, B: SGC-7901 cells. Results are expressed as mean ± SD (n = 3) of three independent experiments. a, b, c, d, e: Statistically different when compared with each other as analyzed by Tukey multiple comparison test (P < 0.05)
Fig. 3. The apoptosis rate of GES-1 cells and SGC-7901 cells were determined by FCM with annexin V-FITC and PI double labeling. A: GES-1 cells; B: SGC-7901 cells, date from one of three experiments with similar results are presented. 1 − 4: control (the control group cells were maintained in RPMI 1640 medium and did not treated with any drugs), capsaicin, dihydrocapsaicin, 6-gingerol; X-axis: Annexin V-FITC log flour, Y-axis: PI log flour; C: Apoptosis index: the percentage of apoptotic cells in total cells. Results are expressed as mean ± SD (n = 3) of three independent experiments. *Statistically different when compared with control as analyzed by Dunnett test (P < 0.05).
Discussion

Various types of cancer chemotherapeutic agents including naturally occurring and synthetic compounds have been studied for efficacy in vitro and in vivo. Recent epidemiological data suggests the ability of capsaicin to inhibit events associated with the initiation, promotion and progression of cancer (Lee, 1995; Modly et al., 1986; Surh and Teel, 1991; Yoshitani et al., 2001). Here, a set of capsaicin analogs (Fig. 2) with some structural modifications were developed to study the relationship between structure and activity.

In the present study, we found that capsaicin analogs were antiproliferative agent against human gastric cancer cells and were toxic to normal human gastric cells. Capsaicin, dihydrocapsaicin, 6-gingerol, vanillin and vanillylamine could all prevent GES-1 and SGC-7901 cell proliferation, cause cell death. The orderly effectiveness of capsaicin analogs was dihydrocapsaicin > capsaicin > 6-gingerol > vanillin ≥ vanillylamine. Dihydrocapsaicin was more cytotoxic compound than capsaicin in HCT116, MCF-7 and WI38 cell lines (Oh et al., 2009), our results is agreed with that of the author’s. Dihydrocapsaicin-induced cytotoxicity was higher in WI38 normal lung epithelial fibroblast cells than in H460 and A549 lung cancer cells (Choi et al., 2010), however, our results show SGC-7901 cancer cells are more susceptible to dihydrocapsaicin than GES-1 normal cells, these results show cell lines performance differently when treated with dihydrocapsaicin.

We can see dihydrocapsaicin, capsaicin and 6-gingerol and its analogs were increased in a dose-responded manner. As GES-1 cells were given with 10 μg/mL capsaicin, dihydrocapsaicin, and 6-gingerol; the ROS levels shoot up from 75.2 to 107.4, 120.3 and 89.4, respectively; Once SGC-7901 cells were fed with 10 μg/mL capsaicin, dihydrocapsaicin and 6-gingerol the ROS levels shoot up from 54.3 to 111.6, 119.4 and 84.5 respectively. This responding yield implied SGC-7901 cells were more effective than GES-1 cells with respect to capsaicin analogs treatment.

Effects of capsaicin and its analogs on the concentrations of MDA and the activity of antioxidant enzymes in GES-1 and SGC-7901 cells

The relationship of MDA and antioxidant enzymes with the apoptosis induced by capsaicin and its analogs was also analyzed. Both cell lines were treated with capsaicin and its analogs for 24 h; and the MDA, SOD, CAT and GSH-Px levels were then detected. The results showed that SOD and GSH-Px in GES-1 and SGC-7901 cells treated with capsaicin and its analogs were up-regulated. When GES-1 and SGC-7901 cells were treated with 10 μg/mL capsaicin or its analogs, the CAT levels were down-regulated. It was obvious that CAT activity down-regulation was responsible for the accumulation of ROS. Therefore, capsaicin and its analogs-induced apoptosis were correlated with CAT expression rather than with SOD or GSH-Px.

Moreover, concentrations of MDA in GES-1 and SGC-7901 cells were increased once treated with capsaicin and its analogs.
remarkably inhibited GES-1 and SGC-7901 cell proliferation, whereas, vanillin and vanillylamine did not, that is to say when the C region: a hydrophobic hydrocarbon tail is removed, its activity decreased markedly; at the same time, while the functional group -NH- is in place of that -CH2-, take capsaicin and 6-gingerol for example, its activity also significantly decreased. In conclusion, B and C regions are both very indispensable for the activity of anticancer of capsaicin. From Fig. 3, we could identify that capsaicin analogs could induce apoptosis in GES-1 cells and in SGC-7901 cells, but there is not the significant difference between GES-1 cells and SGC-7901 cells in apoptosis index; the MTT results showed SGC-7901 cells are more susceptible to capsaicin. Because cell apoptosis involved in oxidative stress was observed. Hence, the levels of ROS, MDA, SOD, CAT and GSH-Px in cells treated with capsaicin analogs were also determined (Fig. 4 and Fig. 5). The results were illustrated ROS, MDA, antioxidant enzyme and GSH-Px activity was up-regulated though CAT activity was decreased. In A549 cells, DHC downregulated CAT, led to ROS accumulation (Oh, et al., 2009), it’s the same to our results.

ROS activities are the known mediators of intracellular signaling cascades. The excessive production of ROS, such as superoxide anion radical, hydrogen peroxide and the hydroxyl radical, leads to oxidative stress, loss of cell function and ultimately apoptosis or necrosis (Ito et al., 2004; Singh et al., 2005; Shen and Liu, 2006). Normally, ROS are detoxified by nonenzymatic or enzymatic antioxidants in-

Fig. 5. Capsaicin analogs-induced apoptosis is regulated by CAT in GES-1 and SGC-7901 cells. A: GES-1 cells; B: SGC-7901 cells; 1-4: MDA, SOD, CAT, GSH-Px. The control group cells were maintained in RPMI 1640 medium and did not treated with any drugs. Results are expressed as mean ± SD (n = 3) of three independent experiments. *Statistically different when compared with control as analyzed by Dunnett test (P < 0.05).
cluding glutathione, superoxide dismutase (SOD), catalase and peroxidase, which protects cells against oxidative stress (Karihtala and Soini, 2007). Our findings indicated that capsaicin analogs induced apoptosis in human gastric cancer cells was initiated by the generation of ROS. In addition, the down-regulation of CAT activity was also involved in the accumulation of ROS whereas the up-regulation of SOD and GSH-Px activity did not. With regards to the MTT, ROS and CAT assays, it also implied SGC-7901 cells were more impressionable than GES-1 cells while treated with capsaicin analogs.

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