Aloe-emodin-induced apoptosis in human gastric carcinoma cells

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Abstract

The purpose of this study was to investigate the anticancer effect of aloe-emodin, an anthraquinone compound present in the leaves of Aloe vera, on two distinct human gastric carcinoma cell lines, AGS and NCI-N87. We demonstrate that aloe-emodin induced cell death in a dose- and time-dependent manner. Noteworthy is that the AGS cells were generally more sensitive than the NCI-N87 cells. Aloe-emodin caused the release of apoptosis-inducing factor and cytochrome c from mitochondria, followed by the activation of caspase-3, leading to nuclear shrinkage and apoptosis. In addition, exposure to aloe-emodin suppressed the casein kinase II activity in a time-dependent manner and was accompanied by a reduced phosphorylation of Bid, a downstream substrate of casein kinase II and a pro-apoptotic molecule. These preclinical studies suggest that aloe-emodin represents a suitable and novel chemotherapeutic drug candidate for the treatment of human gastric carcinoma.

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1. Introduction

Aloe-emodin is a natural active compound present in the leaves of Aloe vera (Reynolds, 1985). Some studies have indicated that aloe-emodin has a number of biological properties, including antiviral, antimicrobial, and hepatoprotective activities (Eshun and He, 2004). Aloe-emodin has also been reported to exhibit an anticancer activity on neuroectodermal tumors, lung squamous cell carcinoma, and hepatoma cells (Pecere et al., 2000; Lee et al., 2001; Kuo et al., 2002). In addition, aloe-emodin has been shown to inhibit S-phase progression in a transformed glia cell line and in a human glioma cell line, sensitize HeLa cells to As2O3 via the generation of reactive oxygen species, and affect the anticancer activity of cisplatin through blocking the activation of extracellular signal-regulated kinase (Acevedo-Duncan et al., 2004; Yi et al., 2004; Mijatovic et al., 2005). However, the effect of aloe-emodin on human gastric cancer cells has not yet been studied.

Apoptosis is an actively regulated process of cell death and the intrinsic pathway of apoptosis involves mitochondria (Penninger and Kroemer, 2003). Mitochondrial outer membrane permeabilization in response to cell death triggers (e.g., DNA damage) is an important early step which is regulated by Bel-2 and controls the release of proteins, such as cytochrome c, from the mitochondria to the cytoplasm where they initiate apoptosis, ultimately leading to cell death (Kim et al., 2006). Apoptosis-inducing factor, another mitochondrial protein that is released into the cytosol and nucleus, induces chromatin condensation and DNA fragmentation (Susin et al., 1999). Most likely,
members of caspase superfamily will be produced and activated that will hasten the cell death process involving the caspase-dependent apoptotic pathway (Kim et al., 2006).

Casein kinase II is a conserved and ubiquitous protein serine/threonine kinase engaged in various functions, including normal and abnormal cell proliferation (Kikkawa et al., 1992). Remarkable, casein kinase II is localized in both the cytoplasm and the nuclear compartment of healthy cells, but is predominantly present in the nuclear compartment of cancer cells and basically deregulated in all carcinoma studied to date (Ahmad et al., 2005). Recent evidence links casein kinase II to apoptosis (Ahmed et al., 2002). A role of casein kinase II in the modulation of caspase susceptibility has been observed with Bid, a proapoptotic member of the Bcl-2 family. It was shown that casein kinase II could phosphorylate Bid, close to the caspase-8 cleavage site, thereby preventing cells from undergoing apoptosis (Desagher et al., 2001). Thus, casein kinase II is an important target for the treatment of cancer as disruption of the casein kinase II activity prevents the phosphorylation of Bid thereby allowing the cleavage of Bid by caspases followed by apoptosis (Ahmad et al., 2005; Unger et al., 2004). Interestingly, an extensive downregulation of casein kinase II by antisense casein kinase II in prostate cancer xenografts eventually led to a complete disappearance of the tumor (Ahmad et al., 2005).

Here, we employed two distinct human gastric carcinoma cell lines, AGS and NCI-N87, representative for the diffuse type and intestinal type of gastric carcinoma, respectively, to evaluate the anticancer effect of aloe-emodin. Observation of nuclei and cell morphologies, and examination of releases of apoptosis-inducing factor and cytochrome c demonstrated the apoptotic activity of aloe-emodin. The role of casein kinase II in aloe-emodin-induced apoptosis was also examined. We report for the first time that the natural compound aloe-emodin can induce apoptosis in human gastric carcinoma cells.

2. Materials and methods

2.1. Aloe-emodin

Aloe-emodin (1,8-dihydroxy-3-[hydroxymethyl]-anthraquinone, CAS registry Number 481-72-1, EU number 2075717, purity ≥ 95%) was purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). It was dissolved in 1% dimethylsulfoxide (DMSO) to a concentration of 7.4 mM purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). It was disolved in 1% dimethylsulfoxide (DMSO) to a concentration of 7.4 mM and stored at −20°C until used.

2.2. Cell culture and treatments

Human gastric carcinoma cell lines (AGS and NCI-N87) were obtained from the Food Industry Research and Development Institute (Hsinchu, Taiwan). Cells were cultured in RPMI-1640 supplemented with 10% heat-inactivated fetal bovine serum (Moregato BioTech, Bulimba QLD, Australia), 100 units/mL penicillin G, 100 µg/mL streptomycin sulfate, and 250 ng/mL amphotericin B (all from Sigma–Aldrich Co.). Both cell lines were grown at 37°C in a humidified atmosphere containing 5% CO2. Prior to treatment, the cells were grown to 90–90% confluence and starved by incubation in basal medium (100% RPMI-1640) for 24 h. In this study, the concentrations (0–0.19 mM in basal medium) and durations (0, 6, 12, 24, 48 and 72 h) of aloe-emodin treatment chosen were based on previous studies (Pecere et al., 2000; Jing et al., 2002).

2.3. Cell viability assay

The cell viability was assessed using XTT (sodium 3-[1-(phenylamino-carbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)benzene-sulfonic acid hydrate) assay kit (Sigma–Aldrich Co.), according to the instructions of the manufacturer. The assay was conducted three times, independently.

2.4. Hoechst 33258 staining

Hoechst 33258 staining was performed as previously described (Lin et al., 2005). Hoechst 33258-positive nuclei were visualized and photographed using an Olympus fluorescence microscope (Olympus, Tokyo, Japan).

2.5. Isolation of mitochondria and extraction of mitochondrial proteins

Mitochondria were isolated using a cell mitochondria isolation kit (Sigma–Aldrich Co.), according to the instructions of the manufacturer with minor modifications. Briefly, treated cells were harvested, resuspended in Lysis Buffer, containing a protease inhibitor cocktail (Sigma–Aldrich Co.), and incubated on ice for 1 min. 1× Extraction Buffer A, containing a protease inhibitor cocktail, was added and the solution was centrifuged at 600g for 10 min at 4°C. The supernatant (containing mitochondria) was carefully transferred to a fresh tube and centrifuged at 11,000g for 10 min at 4°C. Then, the cytosolic fraction was carefully removed to a new tube. Mitochondrial proteins were extracted by suspending the pellet in CellLytic M Cell Lysis Reagent with protease inhibitor cocktail (Sigma–Aldrich Co.). The samples were stored at −80°C until used. The protein content of the cytosolic and mitochondrial fractions were determined using a BCA protein assay kit (Pierce Biotechnology, Inc., Rockford, IL, USA) with bovine serum albumin as a standard.

2.6. Total protein preparation

Total proteins were extracted with an M-PER mammalian protein extraction reagent (Pierce Biotechnology, Inc.), according to the instructions of the manufacturer. The samples were stored at −80°C until used. The protein concentration was measured as described above.

2.7. Immunoblotting

Denatured protein samples were subjected to 15% SDS-PAGE. Proteins were transferred to nitrocellulose membranes. Blocked blots were incubated for 1 h at room temperature with the primary antibodies: monoclonal anti-apoptosis-inducing factor (E-1) and monoclonal anti-cytochrome c (A-8) (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), and polyclonal anti-phospho Bid-Ser61 (Bethyl Laboratories, Inc., Montgomery, TX). Monoclonal anti-Bcl-2 (Abcam Ltd., Cambridge, UK) was used as a control for equal protein loading. Blots were further incubated with secondary antibodies conjugated with alkaline phosphatase for 1 h at room temperature, then incubated with Lumi-Phos WB Chemiluminescent substrate (Pierce Biotechnology, Inc.), and exposed to a Fuji medical X-ray film (Fuji Photo Film Co., Tokyo, Japan). Image processing was performed using the software Fuji Image Gauge. All the experiments were conducted three times, independently.

2.8. Caspase-3 activity assay

The caspase-3 activity was determined using a caspase-3 assay kit (Sigma-Aldrich Co.). The caspase-3 inhibitor N-acetyl–Asp–Glu–Val–
Asp–CHO (Ac-DEVD-CHO; Biomol Research Laboratories, Plymouth, PA, USA) was co-treated with aloe-emodin at a final concentration of 200 μM to inhibit caspase-3 activity in a parallel experiment (Chatterjee et al., 2004). The assay was conducted three times, independently.

2.9. Casein kinase II activity assay

Casein kinase II activity was measured using a casein kinase assay kit (Sigma–Aldrich Co.) combined with the PKLight HTS protein kinase assay kit (Cambrex Bio Science Rockland, Inc., Rockland, MA, USA). Briefly, after aloe-emodin treatment, casein kinase II substrate α-casein and reaction buffer containing ATP (both from casein kinase assay kit) were added to the cell lysates and incubated at 37 °C for 15 min. The remaining ATP was further consumed by luciferase and light was generated from ATP and luciferin (luciferase and luciferin were from PKLight HTS protein kinase assay kit). The bioluminescence was measured using a luminometer (Berthold Detection Systems, Oak Ridge, TN, USA). The PKLight HTS protein kinase assay kit measures the consumption of ATP and is based on the bioluminescent measurement of the remaining ATP present in the samples after kinase activity. The bioluminescent signal is inversely proportional to the activity of the kinase, that is, a higher value is indicative for an increased amount of remaining ATP and a lower casein kinase II activity in the cells. The assay was conducted three times, independently.

2.10. Statistical analysis

The unpaired Student’s t-test was used to identify means that were significantly different from each other (P < 0.05).

3. Results

3.1. Aloe-emodin induces cell death in a dose- and time-dependent manner

The effect of aloe-emodin on the viability of AGS and NCI-N87 gastric carcinoma cells was examined using the XTT viability assay. Exposure of AGS cells to various concentrations of aloe-emodin (i.e., 0.07, 0.11, 0.15, and 0.19 mM) resulted in a dose- and time-dependent decrease in cell viability relative to control cell cultures (Fig. 1a). The IC₅₀ value for 72 h of exposure to aloe-emodin was below 0.07 mM. A similar effect of aloe-emodin was observed after 48 or 72 h incubation using the NCI-N87 cell line (Fig. 1a). In the latter case, however, the IC₅₀ value for a 72-h exposure to aloe-emodin was between 0.15 and 2298

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Fig. 1. Aloe-emodin is cytotoxic to and induces apoptosis in the AGS and NCI-N87 gastric carcinoma cell lines. The cells were incubated with different concentrations of aloe-emodin for 48 and 72 h. (a) Survival curve of AGS and NCI-N87 cells. The percentage of viable cells was calculated by defining the viability of cells without aloe-emodin treatment as 100%. The results are the means ± S.D. of three independent experiments. Means that are significantly different from the respective control values are indicated with * (P < 0.05) and ** (P < 0.01). (b) After treatment with 0.15 mM aloe-emodin for 48 h, apoptotic cells were detected by Hoechst 33258 staining and examined by fluorescence microscopy. The representative images of three independent experiments are shown. Upper panels: AGS cells; Lower panels: NCI-N87 cells. Magnification: 400×.
0.19 mM, suggesting that the AGS cells are more sensitive to aloe-emodin than the NCI-N87 cells. Aloe-emodin-induced cell death was significant at a concentration of 0.15 mM which tempted us to apply this concentration for all further experiments. As aloe-emodin is initially dissolved in 1% DMSO, AGS and NCI-N87 cells were treated with a similar amount of DMSO in a control experiment. No detectable effect of this DMSO concentration was observed in any of the two gastric cell lines (data not shown).

3.2. Aloe-emodin-induced apoptosis in AGS and NCI-N87 cells

To further investigate whether the aloe-emodin-mediated cell death in AGS and NCI-N87 cells was due to an apoptotic mechanism, the nuclear morphological changes that occurred during aloe-emodin treatment were observed. Treatment of AGS cells with 0.15 mM aloe-emodin for 48 h resulted in changes in the nuclear morphology as evidenced by the Hoechst 33258 staining (Fig. 1b), a dye which is often used to label DNA in living cells (Martin et al., 2005) and to observe morphological and nuclear changes (Lin et al., 2005; Sharma et al., 2006). More fragmented nuclei were observed upon aloe-emodin treatment, both in the AGS as in the NCI-N87 cells. These observations illustrated that aloe-emodin-induced cell death in AGS and NCI-N87 cells involved a typical apoptotic pathway.

3.3. Aloe-emodin induces the release of apoptosis-inducing factor and cytochrome c

The release of apoptosis-inducing factor and cytochrome c in AGS and NCI-N87 cells upon treatment with aloe-emodin was characterized because these processes are typically related to apoptosis (Ahmed et al., 2002). Immunoblot analysis of the mitochondrial and cytosolic fractions derived from aloe-emodin-treated AGS and NCI-N87 cells revealed a significant decrease in the amount of apoptosis-inducing factor and cytochrome c in mitochondrial fractions and an increase of apoptosis-inducing factor and cytochrome c in the cytosolic fraction for indicated time intervals (Fig. 2). Upon treatment of AGS cells, the release of apoptosis-inducing factor and cytochrome c commenced at 6 and 12 h, respectively, in contrast to NCI-N87 cells, in which the releases of apoptosis-inducing factor and cytochrome c started after 24 h of treatment. These results were consistent with the cell viability data and confirm that AGS cells were more sensitive to aloe-emodin than NCI-N87 cells.

3.4. Effect of aloe-emodin on the activation of caspase-3

The involvement of caspase-3 in aloe-emodin-induced apoptosis in AGS and NCI-N87 cells was evaluated. The activity of caspase-3 was significantly induced 24 h after aloe-emodin treatment in AGS cells (Fig. 3a). This effect was also observed in NCI-N87 cells albeit only significantly after 48 h of aloe-emodin treatment (Fig. 3a). To illustrate the sequence of caspase-3 activation and the release of apoptosis-inducing factor and cytochrome c, time course of caspase-3 activation after aloe-emodin treatment was performed in AGS cells. As shown in Fig. 3b, caspase-3 activity was significantly induced after 12 h of aloe-emodin treatment. The results suggested that the release of apoptosis-inducing factor and cytochrome c started before caspase-3 activation. To demonstrate whether activation of caspase-3 is essential for aloe-emodin-mediated apoptosis, the influence of the peptidyl inhibitor of caspase-3, Ac-DEVD-CHO, which is a generally used caspase-3 inhibitor, was analyzed. Aloe-emodin-induced caspase-3 activation in AGS cells was blocked when co-treated with Ac-DEVD-CHO (Fig. 3b). These data demonstrate that activation of caspase-3 is an essential step in aloe-emodin-induced apoptosis in both cell lines, however, the NCI-N87 cells

![Fig. 2. Aloe-emodin induces the release of apoptosis-inducing factor and cytochrome c (cyt c) in AGS and NCI-N87 cells. Cells were incubated with or without 0.15 mM aloe-emodin for 0, 6, 12, 24, and 48 h. Mitochondrial (mito) and cytosolic (cyto) fractions were analyzed by 15% SDS-PAGE and probed with primary antibodies as described (Section 2). Results are representative of three independent experiments.](image-url)
3.5. The effect of aloe-emodin on casein kinase II activity and Ser61 phosphorylation of Bid

To investigate the role of casein kinase II in aloe-emodin-induced apoptosis, the activity of casein kinase II was examined as well as Ser61 phosphorylation of Bid, a downstream substrate of casein kinase II (Ser61 is one of the phosphorylation sites of Bid). The activity of casein kinase II started to decrease at 6 h of exposure to aloe-emodin and continued to decrease in a time-dependent manner in AGS cells (Fig. 4a). A similar effect was observed in the NCI-N87 cells (Fig. 4a); however, the activity of casein kinase II started to decrease after 24 h of exposure to aloe-emodin. Immunoblotting using anti-phospho Bid-Ser61 polyclonal antibodies was used to confirm the kinase activity. The aloe-emodin-mediated inhibition of casein kinase II activity caused an inhibition of Ser61 phosphorylation of Bid.
Bid (Fig. 4b). These results suggest that aloe-emodin might induce apoptosis in AGS and NCI-N87 cells through inhibition of the phosphorylation of Bid.

4. Discussion

In the present study, we demonstrated that aloe-emodin has an anticancer activity on AGS and NCI-N87 gastric carcinoma cells and that the cytotoxic mechanism involves the induction of apoptosis. The latter was characterized by a release of apoptosis-inducing factor and cytochrome c from the mitochondria to the cytosol, activation of caspase 3, and inhibition of the activity of casein kinase II, and thus of downstream phosphorylation of Bid. Using the human lung squamous carcinoma cell line CH27, it was described that apoptosis induced by aloe-emodin was associated with changes of the expression of members of the Bcl-2 family apoptosis regulators (i.e., increase of the Bax level and decrease of Bcl-XL). It was also found that aloe-emodin caused cytochrome c release from mitochondria (Lee, 2001). In addition, it was observed that aloe-emodin-induced apoptosis in human hepatocellular carcinoma cell lines, HepG2 and Hep3B, was accompanied by the induction of p53 and p21 expression (Kuo et al., 2002). Another report describes the decrease in the expression of protein kinase Cβ and ε isoforms that may play a critical role in aloe-emodin-induced apoptosis (Lee, 2001). A similar role of protein kinase C was observed in U-937 glioma cells (Acevedo-Duncan et al., 2004). With the exception of protein kinase Cα, most of the protein kinase C isozymes (protein kinase Cα, βI, γ, δ, ε, θ, ξ, and μ) declined upon aloe-emodin treatment. Interestingly, two hydrophobic residues unique to casein kinase II, Val66 and Ile174, seem to be essential for the interaction with aloe-emodin as, for instance, a Val66 Ala casein kinase II variant exhibited a substantially affected interaction with aloe-emodin (Sarno et al., 2002; Litchfield, 2003).

In our study, aloe-emodin-induced apoptosis in gastric carcinoma cells involves inhibition of casein kinase II activity and blockage of the phosphorylation of Bid. We have also demonstrated that aloe-emodin caused the release of apoptosis-inducing factor and cytochrome c from mitochondria, followed by the activation of caspase-3. It is known that phosphorylated Bid can be cleaved by caspase-8, and truncated Bid can bind to mitochondria to induce the release of apoptosis-inducing factor and cytochrome c from mitochondria (Chau et al., 2007; Shulga and Pastorino, 2006; Kim et al., 2006). It is also known that, in the cytosol, cytochrome c mediates the allosteric activation of Apf-1, which is required for the proteolytic maturation of caspase-9 and caspase-3 (Garrido et al., 2006; Kim et al., 2006). We think that inhibition of casein kinase II activity after aloe-emodin treatment can lead to activation of caspase-3 through phosphorylation of Bid, release of apoptosis-inducing factor and cytochrome c from mitochondria. A rather similar pathway has been described for Radix-Paeoniae-Alba-extract-induced apoptosis in HL-60 leukemic cells and for quercitin-mediated cell apoptosis in murin melanoma B16-BL6 cells (Kwon et al., 2006; Zhang et al., 2005). Ahmad et al. (2006) described that downregulation of casein kinase II by antisense RNA elicited intracellular hydrogen peroxide production, and that hydrogen peroxide production was associated with caspase-3 activation. Although not relative to aloe-emodin, it is another possible pathway between casein kinase II and caspase-3. Further studies are needed for more detailed understanding of the relationship between casein kinase II activity and caspase-3 activity.

It is noteworthy that in all assays used, the AGS gastric carcinoma cells, representing the diffuse type gastric cancer, are significantly more sensitive to aloe-emodin than the NCI-N87 cells that are representative for the intestinal type of gastric carcinoma. The reason for this difference in sensitivity remains unclear. Some controversial data aim to correlate differences in response to a given drug with the differentiation state of a given cell line. In an in vitro system using epidermal cells, maturing basal cells underwent apoptosis upon drug treatment, whereas stem cells seem to be resistant (Morris et al., 1990). In addition, it has been suggested that undifferentiated keratinocyte stem cells are protected from spontaneous apoptosis (Tiberio et al., 2002). Similarly, differentiated human neural crest-derived tumor cells exhibit an increased resistance to potassium ionophore-mediated apoptosis as compared to undifferentiated cells and human keratinocytes that are undifferentiated are more sensitive to H2O2-induced cell death than their differentiated counterparts (Teplova et al., 2004; Zuliani et al., 2005). However, it has recently been demonstrated that TNF-related apoptosis-inducing ligand triggers apoptosis in undifferentiated but not in differentiated human keratinocytes (Jansen et al., 2003). Microscopy analyses demonstrated a different cell morphology and growth pattern between AGS and NCI-N87 cells (data not shown). The AGS cells were less differentiated and arranged in a cohesive pattern without a glandular structure. Signet-ring cells are occasionally observed in the AGS cell line. In contrast, the NCI-N87 cells were differentiated and growing according to a nesting pattern characterized by a glandular structure. Based on the Lauren classification which is widely used for the histological typing of gastric carcinoma, the AGS cells were classified as a diffuse type carcinoma whereas the NCI-N87 cells belonged to the intestine type carcinoma. Thus, our results strongly suggest that the degree of differentiation of gastric carcinoma cells affects the cellular response to aloe-emodin. In other words, the less-differentiated gastric carcinoma cells were more sensitive than the well-differentiated cells which implicate that aloe-emodin might be more effective against gastric carcinoma of the diffuse type than against gastric carcinoma of the intestinal type. In addition to the degree of differentiation of culture cells, there was evidences showed that p53-mutant cell lines were less sensitive to aloe-emodin than p53 wild type cell lines (Perece et al., 2003). In this study, we have measured the amount of mutant p53 in
AGS and NCI-N87 cells. The results showed that the amount of mutant p53 in NCI-N87 cells was 5 times higher than that in AGS cells (1.05 ng/mL and 0.16 ng/mL cell lysate, respectively). Our data are consistent with the previous study and suggest that p53 phenotype can affect the cellular response to aloe-emodin.

Although generally well tolerated, the *Aloe vera* gel induced some burning and mild itching in some individuals (Eshun and He, 2004). Remarkably, aloe-emodin did not cause any detectable acute or chronic toxic effects in various normal cell lines and in animal model systems (Pecere et al., 2000). A selective uptake of aloe-emodin by neuroectodermal tumor cells, but not by other tumor cells tested, was observed (Pecere et al., 2000). Nevertheless, a detailed investigation of the effects of aloe-emodin on normal healthy cells in a human body still needs to be performed. In addition, in order to use aloe-emodin as a chemotherapeutic agent to ameliorate specific types of human carcinoma, it might be a challenge to engineer methods that allow the specific and efficient delivery of aloe-emodin to a given tumor in a human body. Further, engineering of the 50-nm-diameter nanocapsule that allows the specific delivery of antisense casein kinase II to tumor cells but not to other cells might be useful in this respect (Ahmad et al., 2005).

In conclusion, we have used two human gastric carcinoma cell lines to study the anticancer effect of the natural product, aloe-emodin, isolated from *Aloe vera* leaves, and demonstrated for the first time that aloe-emodin exhibits an anticancer effect against gastric carcinoma. Its unique cytotoxicity profile together with its promising inventory of anticancer activities strongly suggest that aloe-emodin can be used as a chemotherapeutic drug candidate for the treatment of gastric carcinoma of the diffuse type and most likely also other types of human carcinoma. Future studies are to focus on a better understanding of the exact mode of action of aloe-emodin and the cause-effect relationship in order to prepare for the first clinical studies and trials that will evaluate the effect of aloe-emodin in cancer patients.

5. Conflict of interest statement

None declared.

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