

## Bibliography

### Aloe –emodin a noval antitumor chemotherapeutic drug

English Title: Aloe-emodin modulates PKC isozymes, inhibits proliferation, and induces apoptosis in U-373MG glioma cells.

Personal Authors: Acevedo-Duncan, M., Russell, C., Patel, S., Patel, R.

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Editors: No editors

Document Title: International Immunopharmacology, 2004 (Vol. 4) (No. 14) 1775-1784

#### Abstract:

Aloe-emodin (1,8-dihydroxy-3-[hydroxymethyl]-anthraquinone) purified from *Aloe vera* leaves has been reported to have antitumor activity. The objectives of our research were to determine how aloe-emodin regulates the cell cycle, cell proliferation and protein kinase C (PKC) during glioma growth and development. To establish the cell cycle effects of aloe-emodin on brain cells [transformed glia cell line (SVG) and human glioma U-373MG cell line (U-373MG)], cells were treated with either dimethylsulfoxide (DMSO; control) or aloe-emodin (40 µM). Results from flow cytometry demonstrated that aloe-emodin delayed the number of cells entering and exiting DNA synthesis (S) phase in both SVG and U-373MG cells indicating that aloe-emodin may inhibit S phase progression. Assessment of cell viability demonstrated that SVG and U-373MG glioma cell were highly sensitive to aloe-emodin. The aloe-emodin-induced decreased proliferation was sustained at 48-96 h. A PKC activity assay was quantified to establish the role of PKC in aloe-emodin's mode of action. Exposure of SVG and U-373MG glioma cells to aloe-emodin suppressed PKC activity and reduced the protein content of most of the PKC isozymes. We determined that cancer growth inhibition by aloe-emodin was due to apoptosis (i.e., programmed cell death). Taken together, these results support the hypothesis that aloe-emodin represents a novel antitumor chemotherapeutic drug.

Publisher: Elsevier Science B.V.

### Aloe-emodin inhibited N-acetylation and DNA adduct of 2-aminofluorene and arylamine N-acetyltransferase gene expression in mouse leukemia L 1210 cells

**Authors:** Chung J.-G.<sup>1</sup>; Li Y.-C.; Lee Y.-M.; Lin J.-P.; Cheng K.-C.; Chang W.-C.

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# Aloe-emodin anticancer effects in two human liver cancer cell lines Hep G2 and Hep 3B.

These findings suggest that aloe-emodin may be useful in liver cancer prevention.

## Revue / Journal Title

### Titre du document / Document title

The antiproliferative activity of aloe-emodin is through p53-dependent and p21-dependent apoptotic pathway in human hepatoma cell lines

### Auteur(s) / Author(s)

KUO Po-Lin ; LIN Ta-Chen ; LIN Chun-Ching ;

### Résumé / Abstract

The aim of this study is to investigate the anticancer effect of aloe-emodin in two human liver cancer cell lines, Hep G2 and Hep 3B. We observed that aloe-emodin inhibited cell proliferation and induced apoptosis in both examined cell lines, but with different the antiproliferative mechanisms. In Hep G2 cells, aloe-emodin induced p53 expression and was accompanied by induction of p21 expression that was associated with a cell cycle arrest in G1 phase. In addition, aloe-emodin had a marked increase in Fas/APO1 receptor and Bax expression. In contrast, with p53-deficient Hep 3B cells, the inhibition of cell proliferation of aloe-emodin was mediated through a p21-dependent manner that did not cause cell cycle arrest or increase the level of Fas/APO1 receptor, but rather promoted aloe-emodin induced apoptosis by enhancing expression of Bax. These findings suggest that aloe-emodin may be useful in liver cancer prevention.

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## Anticancer effects of aloe-emodin on HepG2 cells: Cellular and proteomic studies

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### ABSTRACT

Aloe-emodin (AE) is one of the main bioactive anthraquinones of *Rheum palmatum*, a widely used herbal medicine. Several recent studies suggested that AE possesses potent anticancer properties, although the mechanisms are yet to be fully elucidated. The present study aimed to identify the molecular targets of AE in a human hepatocellular carcinoma cell line, HepG2. Aloe-emodin (AE) is one of the main bioactive anthraquinones of *Rheum palmatum*, a widely used herbal medicine. Several recent studies suggested that AE possesses potent anticancer properties, although the mechanisms are yet to be fully elucidated. The present study aimed to identify the molecular targets of AE in a human hepatocellular carcinoma cell line, HepG2. We first found that AE was more cytotoxic and effective in inducing apoptosis and cell cycle arrest than its analog emodin (EM). Proteomic study using 2-D DIGE revealed that AE affected multiple proteins associated with oxidative stress, cell cycle arrest, antimetastasis, and hepatitis C virus replication. For example, peroxiredoxins (PRDX) and DJ-1, both of which are redox-sensitive proteins, were among those markedly up-regulated, suggesting the presence of oxidative stress in AE-treated cells. Further biochemical studies demonstrated that AE enhanced the intracellular level of reactive oxygen species and oxidation of PRDX-2, -4, and DJ-1. In addition, AE inhibited DNA synthesis *via* up-regulation of the CDK4 inhibitor p16 and inhibition of Rb phosphorylation. Furthermore, AE was able to decrease cell migration *via* up-regulation of the metastasis inhibitor,

nm23. Taken together, AE induced anticancer effects in HepG2 cells *via* multiple pathways by affecting different protein targets.

# **Aloe emodin inhibits the cytotoxic action of tumor necrosis factor**

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## **Abstract**

We demonstrate the capacity of an herbal anthraquinone aloe emodin to reduce the cytotoxicity of the proinflammatory cytokine tumor necrosis factor (TNF) towards L929 mouse fibrosarcoma and U251 human glioma cell lines. Aloe emodin inhibited both TNF-induced cell necrosis and apoptosis, but it did not reduce cell death induced by UV radiation or hydrogen peroxide. Aloe emodin inhibited both basal and TNF-triggered activation of extracellular signal-regulated kinase (ERK), and a selective blockade of ERK activation mimicked the cytoprotective action of the drug. On the other hand, aloe emodin did not affect TNF-induced activation of p38 mitogen-activated protein kinase or

generation of reactive oxygen species. The combination of aloe emodin and TNF caused an intracellular appearance of acidified autophagic vesicles, and the inhibition of autophagy with bafilomycin or 3-methyladenine efficiently blocked the cytoprotective action of aloe emodin. These data indicate that aloe emodin could prevent TNF-triggered cell death through mechanisms involving induction of autophagy and blockade of ERK activation.

**Keywords:** Aloe emodin; Tumor necrosis factor; Cytotoxicity; Apoptosis; Necrosis; Autophagy; Extracellular signal-regulated kinase

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utophagy; Extracellular signal-regulated kinase

## **Aloe-emodin Is a New Type of Anticancer Agent with Selective Activity against Neuroectodermal Tumors<sup>1</sup>**

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### **Abstract**

**Here we report that aloe-emodin (AE), a hydroxyanthraquinone present in *Aloe vera* leaves, has a specific *in vitro* and *in vivo* antineuroectodermal tumor activity. The growth of human neuroectodermal tumors is inhibited in mice with severe combined immunodeficiency without any appreciable toxic effects on the animals. The compound does not inhibit the proliferation of normal fibroblasts nor that of hemopoietic progenitor cells. The cytotoxicity mechanism consists of the induction of apoptosis, whereas the selectivity against neuroectodermal tumor cells is founded on a specific energy-dependent pathway of drug incorporation. Taking into account its unique cytotoxicity profile and mode of action, AE might represent a conceptually new lead antitumor drug.**

### **Introduction**

With the aim of developing novel anticancer drugs characterized by selective targeting and low toxicity for dividing normal host tissues, we devoted our attention to a number of natural compounds that have traditionally been used to treat a variety of diseases for hundreds of years (1–3). We assayed only those natural compounds that have already been proven to be nontoxic, and we evaluated their efficacy against highly malignant tumors that are not normally included in the classical screening assays, *i.e.*, pPNET,<sup>3</sup> Ewing's sarcoma, and neuroblastoma. The last of these is the most common solid extracranial tumor in infants, accounting for 10% of all childhood cancers. At the time of diagnosis, ;50% of affected children have disseminated neuroblastoma disease with a very poor prognosis that has remained unchanged in the last 3 decades (4, 5). Our study analyzed the cytotoxic potential of AE, a hydroxyanthraquinone (Fig. 1A) naturally present in the leaves of *Aloe vera* (6, 7). This report describes the selective *in vitro* and *in vivo* killing of neuroectodermal tumor cells by AE, the anticancer activity of which is based on apoptotic cell death,

promoted by a tumor cell-specific drug uptake process that may offer opportunities for novel anticancer agents.

## Aloe-Emodin Quinone Pretreatment Reduces Acute Liver Injury Induced by Carbon Tetrachloride

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**Source:** *Basic & Clinical Pharmacology & Toxicology*, Volume 87, Number 5, 1 November 2000, pp. 229-233(5)

**Publisher:** Blackwell Publishing

### Abstract:

Aloe contains several active compounds including aloin, a C-glycoside that can be hydrolyzed in the gut to form aloe-emodin anthrone which, in turn, is auto-oxidized to the quinone aloe-emodin. On the basis of the claimed hepatoprotective activity of some anthraquinones, we studied aloe-emodin in a rat model of carbon tetrachloride (CCl<sub>4</sub>) intoxication, since this xenobiotic induces acute liver damage by lipid peroxidation subsequent to free radical production. Twelve rats were treated with CCl<sub>4</sub> (3 mg/kg) intraperitoneally and six were protected with two intraperitoneally injections of aloe-emodin (50 mg/kg; CCl<sub>4</sub>+aloe-emodin); six other rats were only aloe-emodin injected (aloe-emodin) and six were untreated (control). Histological examination of the livers showed less marked lesions in the CCl<sub>4</sub>+aloe-emodin rats than in those treated with CCl<sub>4</sub> alone, and this was confirmed by the serum levels of L-aspartate-2-oxoglutarate-aminotransferase (394±38.6 UI/l in CCl<sub>4</sub>, 280±24.47 UI/l in CCl<sub>4</sub>+aloe-emodin rats; P<0.05). We also quantified changes in hepatic albumin and tumour necrosis factor- $\alpha$  mRNAs. Albumin mRNA expression was significantly lower only in the liver of CCl<sub>4</sub> rats (P<0.05 versus control) and was only slightly reduced in the CCl<sub>4</sub>+aloe-emodin rats. In contrast tumour necrosis factor- $\alpha$  mRNA was significantly higher (P<0.05) in the CCl<sub>4</sub> than the control rats and almost equal in the CCl<sub>4</sub>+aloe-emodin, aloe-emodin and control groups. In conclusion, aloe-emodin appears to have some protective effect not only against hepatocyte death but also on the inflammatory response subsequent to lipid peroxidation.

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## Aloe-emodin suppressed NMDA-induced apoptosis of retinal ganglion cells through regulation of ERK phosphorylation

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### Funded by:

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### ABSTRACT

A high concentration of glutamate in the vitreous body and optic nerves of the eyes activates *N*-methyl-D-aspartate (NMDA) receptors and is toxic to retina ganglion cells (RGCs) in glaucomatous patients. Aloe-emodin sulfates/glucuronides (s/g), the major metabolites of aloe-emodin, was found to be effective in decreasing NMDA-induced apoptosis in RGCs. In order to elucidate the mechanisms, an *in vitro* optic neuropathy model adding NMDA to

N18 RGCs was used in this study. The phosphorylation level of extra-cellular signal-regulated kinase1/2 (ERK1/2), c-Jun *N*-terminal kinase (JNK) and p38 kinase (cytokines-suppressive antiinflammatory drug binding protein kinase) were measured by western blotting and luciferase reporter assay. The results showed that aloe-emodin metabolites significantly decreased the activation of three major mitogen-activated protein (MAP) kinase pathways and the activation of downstream genes in nucleus induced by NMDA, which were verified by the addition of the respective inhibitors. Comparing the effect of the inhibitors of the three MAP kinase pathways, the ERK pathway was found to be the major route of aloe-emodin metabolites in decreasing the apoptosis of NMDA-treated RGCs. Besides, *cfos* rather than *cjun* was the target downstream gene. Aloe-emodin metabolites could regulate the phosphorylation of ERK kinases and it was a promising candidate for NMDA-induced apoptosis of RGCs. Copyright © 2007 John Wiley & Sons, Ltd.