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IS ALOE-EMODIN A NOVEL ANTICANCER DRUG?

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ABSTRACT
Different phytochemicals derived from plants, including anthraquinones, are considered to possess anticancer potential. The anthraquinones are bioactive compounds, which are presented as glycosides in various plants. Some anthraquinones and their derivatives, such as emodin, aloe-emodin, danthron, chrysophanol, physcion, and rhein, demonstrate anticancer properties. Among them, one main bioactive anthraquinone, aloe-emodin (AE) has attracted special attention because of its various pharmacological properties: antineoplastic, laxative, antiviral, antibacterial, antifungal, antiprotozoal, and hepatoprotective. Of particular interest are reports demonstrating its antitumor effect in vitro and in vivo. It has been shown that AE could be a potent anticancer agent for multiple tumor cells suppressing their proliferation via p53 and its downstream p21 pathway and inducing in them cell cycle arrest and apoptosis. Moreover, this natural ingredient also possesses **anti-metastasis, and antiangiogenesis** activities.
It seems that aloe-emodin has a specific antitumor activity and can be recommended as an antitumor chemotherapeutic drug.

Key words: aloe-emodin, anticancer effect.

INTRODUCTION

The bioactive properties of the plants have been used in the medicine for thousands of years. According to the World Health Organization, more than 21 000 plants have been used for medical purposes in the world. Because of the therapeutic characteristics of the anthraquinones they are widely used in pharmaceutical industry. Anthraquinones are many different types: emodin (1,3,8-trihydroxy-6-methylanthraquinone), aloe-emodin (1,8-dihydroxy-3-hydroxyl-methyl anthraquinone), rhein (1,8-dihydroxy- 3-carboxyanthraquinone), chrysophanol (1,8-dihydroxy-3-methyl-anthraquinone), physcion (1,8-drihydroxy-3-methyl-6-methoxyanthraquinone), and danthron (1,8-dihydroxy-9,10-anthraquinone). The molecules of these glycosides consist of two parts: a sugar moiety – glycosyl and non-**sugar** group – **aglycone** or genin. Depending on the oxidation state of the aglycone group, the glycosides are divided into three subgroups: anthrones, anthranols, anthraquinones.

Of particular interest is one natural anthraquinone derivative - aloe-emodin (AE) **(Figure 1).** It is a bioactive compound of leaves of *A. barbadensis Miller*, roots and rhizome of rhubarb (*Rheum palmatum*), seeds of buckthorn (*Rhamnus frangula*) and leaves of the herb senna (*Senna*, *Cassia tora*) and purslane. AE possesses various medical properties **(Table 1).** Recently it is a subject of great interest due to its notable anticancer activity on various tumor cells involving multiple mechanisms: inhibition of cancer cell growth and proliferation, cell cycle arrest, induction of apoptosis, anti-metastasis and antiangiogenic effect, and reinforcement of the immune system (14). The cytotoxic effect of AE appears to be selective towards cancer cells as this compound does not inhibit the proliferation of normal cells (1 15).

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Table 1. *Medicinal properties of aloe-emodin extracted from genus: Rhamnus, Aloe, Rheum, Senna.*

Medicinal properties	Examples of influence	References
Purgative effect	AE from extract of dried leaves of *Cassia tora Linn.* shows significant purgative activity in Wister rats.	(1)
Hepatoprotective effect	AE is capable of preventing induced hepatic damage and/or fibrosis. AE protects liver from carbon tetrachloride (CCl4) induced hepatic damage. AE inhibits hepatic stellate cell activation.	(2,3)
Antibacterial effect	AE isolated from *Aloe-vera* juice, gel and leaves shows inhibitory activity towards Gram-positive bacteria**:** *B. subtilis, M. kristinae, B. cereus, S. aureus, S. epidermidis;* Gram-negative bacteria: *E. coli, P. vulgaris, E. aerogenes, S. sonnei, A. hydrophilia, H. pylori.* AE isolated from *Rhei Rhizoma* and *Rheum palmatum*, inhibits in vitro the growth of *B. subtilis* and *S. aureus.*	(4-6)
Antifungal effect	AE isolated from *Rheum emodi rhizomes* inhibits *Candida albicans, Cryptococcus neoformans, Trichophyton mentagrophytes* and *Aspergillus fumigatus.*	(7)
Antiprotozoa effect	AE inhibits the growth of *Trypanosoma brucei brucei* and *Trypanosoma congolense*	(8,9)
Antiviral effect	AE shows inhibitory activity towards: *Japanese encephalitis virus, enterovirus 71; Herpes simplex virus type 1 and type 2, Varicella-zoster virus, Pseudorabies virus, Influenza virus, adenovirus, and rhinovirus.*	(10-12)
Antitumor effect	AE from seeds of *Rhamnus frangula* shows significant inhibitory activity against P-388 lymphocytic leukemia in mice.	(13)

INHIBITION OF CANCER CELLS PROLIFERATION

AE **has been shown to induce dose- and time-dependent** inhibition of the proliferation of various cancer cells, including human promyelocytic leukemia HL-60 cell line (23), human U87 malignant glioma cells (16), breast cancer cells (1 17),keratinocytes(1 18), bladder cancer cells (19) and many other types of cancer cells.

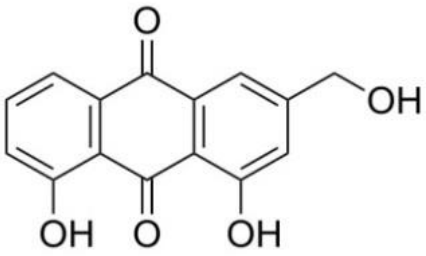

Figure 1. Aloe-emodin (AE) /1,8-Dihydroxy-3-(hydroxymethyl)-9,10-anthraquinone/

CELL CYCLE ARREST

One of the mechanisms via which AE suppresses cancer cells growth is through its ability to impose cell cycle arrest. There are data that the arrest induced by AE depends on the cell type. It has been demonstrated that in human U87 malignant glioma cells AE arrested the cell cycle in the S phase. (20). Through promoted p53, p21 and p27, inhibited cyclin A, E, thymidylate synthase and Cdc25A levels, AE induced also S-phase cell cycle arrest in human tongue squamous cancer SCC-4 cells (21). In hepatoma, leukemia, neuroectodermal cells and v-ras-transformed cells (23) as well as in human colon cancer cells (22) AE induced G2/M cell cycle arrest. Upregulation of p53 and p21 expression is considered to be the mechanism in the induced G2/M cell cycle arrest (23). On the contrary, in human H460 lung nonsmall carcinoma cells, human hepatoma cells and U-373MG glioma cells, AE induced G1/S cell cycle arrest, where p16-Rb-E2F pathway was affected (23).

The activation of cell-cycle arrest followed by apoptosis is a common pathway of AE induced cancer cells death.

APOPTOSIS

The ability to induce apoptosis in multiple cancer cells is the primary cause for the anticancer effect of AE. The mechanism of inducing apoptosis by this agent is not fully understood in different cancer cell lines. In general, it is considered that mitochondrial apoptotic pathway is activated as a result of AE treatment in various cancer cells. Several groups investigated the role of Bcl-2 family proteins in AE induced mitochondrial apoptosis. It is found that anti apoptotic Bcl-2 and Bcl-XL have been downregulated in CH27 and H460 cell as a consequence of AE treatment (23). Moreover, pro-apoptotic Bax and Bak have been upregulated in hepatocellular carcinoma cells (23). In addition, it has been shown that in CH27 cells there is translocation of Bax and Bak from cytosol to mitochondria, which is an initial event in mitochondrial apoptotic pathway (23). In human U87 malignant glioma cells AE promoted the loss of mitochondrial membrane potential which indicated the early event of the mitochondrial apoptotic pathway (24). In human nasopharyngeal carcinoma cells AE induced apoptosis through caspase-8-mediated activation of the mitochondrial death pathway (25). In human tongue squamous carcinoma SCC-4 cells AE induced apoptosis through the Fas/death-receptor, mitochondria and caspase cascade (26). Individual characteristics of different cancer cell types define whether the response of the cells to AE treatments will be apoptosis. For example, the response of mouse B16 melanoma and human skin melanoma (A375) cells to AE was found to be different. Although both cell types were sensitive to AE, the treatment with this **anthraquinone** induced differentiation of mouse cells toward melanocytes, while in human cells induced apoptosis (27).

ANTI-METASTASIS ACTIVITY

It is considered that AE possesses anti-metastasis activity. It inhibited PKC isozymes, P38, and ERKs whose roles in the development of cancer metastasis are well known (23). Furthermore, Lu and co-authors have shown that in HepG2 cells AE upregulated the metastasis-associated inhibitor nm23 and in this way decreased cell migration (28). The ability of AE to inhibit invasion and metastasis also has been shown in high metastatic breast cancer MDA-MB-231 cells (29) as well as in colon cancer cell, WiDr (30). The ability of AE to suppress migration of colon cancer cells was found to be due to downregulation of MMP-2/9, RhoB and VEGF via reduced DNA binding activity of NF-κB.

SENSITIZATION ACTIVITY

Similar to some other anthraquinones, AE also possesses sensitization activity and can sensitize tumor cells toward cisplatin, arsenic and other chemotherapeutic agents. It appears that the increased ROS, generated by AE, play a main role in this synergistic effect via alterations in expression of genes, important for regulation of signal transduction, cell-cycle arrest, and apoptosis (23).

CONCLUSIONS

A number of studies have indicated the activity of AE against various cancer cell types. It seems that this natural anthraquinone inhibits tumor cell growth and induces apoptosis. That involves disruption of **mitochondrial membrane potential and caspase 3 activation.** In the most cell lines the mechanism of induced cell death included AE-induced cell cycle arrest, coupled with upregulation of p53 and p21expression. The observation that tumor cells seem to be more sensitive to AE than normal cells is extremely important. The ability of AE to sensitize tumor cells towards chemotherapeutic agents allows it to be used both separately, and in combination with other chemotherapeutics.

To sum up, although experimental data support the standpoint that this natural compound is a potential anticancer candidate, further research is necessary for pharmaceutical development of AE as a potent, anticancer agent.

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