Biomedicine & Pharmacotherapy 95 (2017) 477–486

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Sweroside eradicated leukemia cells and attenuated pathogenic processes in mice by inducing apoptosis

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ARTICLE INFO

Article history:
Received 15 June 2017
Received in revised form 28 July 2017
Accepted 2 August 2017

Keywords:
Leukemia
Sweroside
G2/M cell-cycle arrest
Apoptosis
Caspase-3

ABSTRACT

Acute myeloid leukemia (AML), characterized by extremely heterogeneous molecular and biologic abnormalities, is an aggressive hematologic malignancy, hampering the research and development of effective targeted treatment modalities. Sweroside (SWE), an iridoid glycoside, is isolated from Lonicera japonIca. It has diverse biological activities, but little is known in human leukemia. Here, our study showed the potential of sweroside as an effective agent against human leukemia using in vitro and in vivo approaches. Sweroside treatment obviously reduced the cell viability in human leukemia cell lines and primary human leukemia cells. S and G2/M cell-cycle arrest were induced by sweroside, associated with the down-regulation of Cyclin D1, cyclin-dependent kinase 4 (CDK4), CDC2 and CDC25 as well as the up-regulation of p53 and p21. In addition, apoptosis was highly induced by sweroside both in vitro and in vivo through enhancement of cleaved Caspase-3 and poly (ADP-ribosyl) transferase (PARP). Consistently, anti-apoptotic molecule of B cell CLL/lymphoma 2 (Bcl-2) was impeded by sweroside, while pro-apoptotic signal of Bcl-2-associated X protein (Bax) was elevated. In vivo, HL-60-bearing tumor growth was considerably inhibited by sweroside, which was related to proliferation suppression and apoptosis induction. Our study highlighted the therapeutic potential of sweroside, and provided new insights into the molecular mechanism of sweroside chemosensitization in human leukemia.

1. Introduction

Acute myeloid leukemia (AML) is reported as one of the most aggressive hematologic malignancies in adults along with 5-year relative survival rates of 8–10% [1,2]. Because the abnormal collection of immature precursors, and the inhibition of normal haemopoiesis, AML represents as a medical emergency, accompanied with a high level of early fatalities from the massive hemorrhage [3–5]. There are no surgical options owing to the body-wide distribution of malignant cells [6]. Thus, currently, chemotherapy is the initial treatment of choice. However, the standard approach to prevent or treat AML has little to be changed in the last four decades and employs the cytotoxic drugs. Most patients with AML will receive a combination of medications [7,8]. Thus, finding effective therapeutic strategies and indicating the underlying molecular mechanisms are urgently required and could be beneficial and useful for patients with leukemia.

It is clearly necessary to find safer and more effective agents because of the potential side effect of chemotherapy [9]. Due to various safety concerns and the lower efficacy of commercially available drugs, the isolation and identification of new compounds from natural sources which have various bio-abilities, including anti-inflammation, anti-oxidant and even anti-cancer, have attracted much interest [10,11]. Lonicera japonica is reported as a popular folk medicine in east Asian countries for the prevention or treatment of various diseases and symptoms, such as fever, colds, pain, enteritis, and swellings [12,13]. It also possesses various pharmacological actions, such as antiviral activity, anti-inflammatory effect and antibacterial activity [14,15]. In the study, we analyzed the inhibitory mechanisms of sweroside (Fig. 1A), an iridoid glycoside, isolated from Lonicera japonica, through in vitro and in vivo system in models of AML.

Here, for the first time, we explored the activity of sweroside against AML as an effective therapeutic strategy. We investigated its mechanism of action in depth using multiple leukemia cell lines, and verified our results and findings in an in-vivo mouse xenograft model.

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http://dx.doi.org/10.1016/j.biopha.2017.08.007
0753-3322/

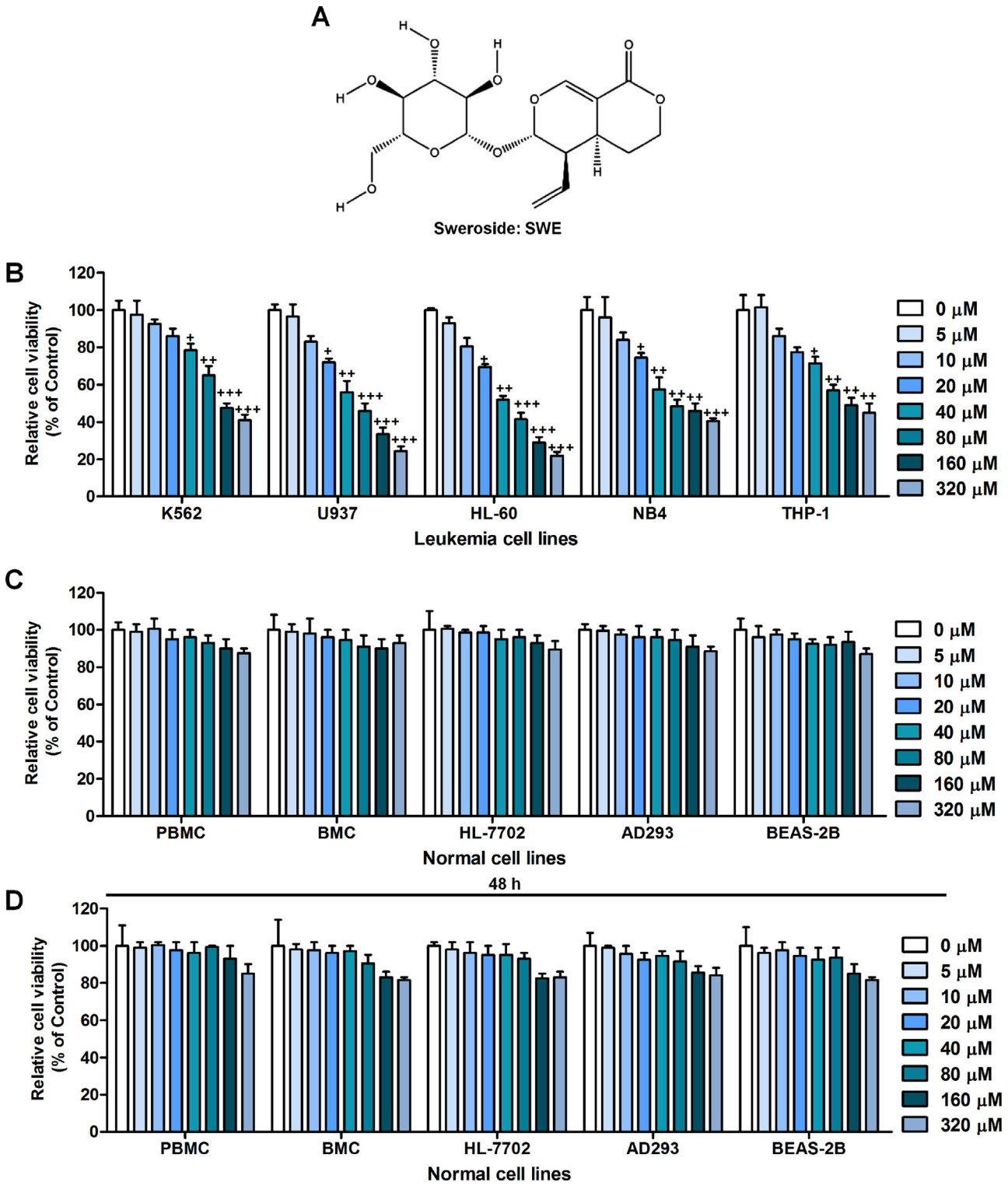

Fig. 1. Sweroside suppresses the proliferation of human leukemia cell lines. (A) The chemical structure of sweroside. (B) Human leukemia cell lines, including K562, U937, HL-60, NB4, and THP-1, were cultured with different concentrations of sweroside (0, 5, 10, 20, 40, 80, 160, and 320 uM) for 24 h. Then, the cell viability was measured using MTT analysis. (C-D) Normal cell lines of normal human peripheral blood mononuclear cells (PBMC) and murine bone marrow cells (BMC), human normal liver cell line of HL-7702, human normal renal line of AD293, and human normal lung cells of BEAS–2 B were all exposed to the indicated doses of sweroside for 24 and 48 h, respectively. Next, the MTT analysis was used to determine the viability of cells. Data are represented as the mean ± SEM, n = 8. $^{+}P < 0.05$, $^{++}P < 0.01$, $^{+++}P < 0.001$ versus the Control group.