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Research paper

Garcinone D, a natural xanthone promotes C17.2 neural stem cell proliferation: Possible involvement of STAT3/Cyclin D1 pathway and Nrf2/HO-1 pathway

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HIGHLIGHTS

- Garcinone D promotes the C17.2 neural stem cell proliferation.
- Garcinone D increases the protein levels of phosphorylated STAT3 and Cyclin D1.
- Garcinone D enhances the protein levels of Nrf2 and HO-1.
- Nrf2 inhibitor partially reverses garcinone D-induced C17.2 cell proliferation.

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ABSTRACT

Garcinia mangostana L. (Mangosteen) has been used to treat various pathological conditions, including inflammation and urinary tract infections. Here, we observed that garcinone D, a natural xanthone from mangosteen, promoted the proliferation of C17.2 neural progenitor cells and also resulted in a larger percentage of cells in S phase compared with the control group. Moreover, garcinone D increased the protein levels of phosphorylated signal transducer and activator of transcription 3 (p-STAT3) and Cyclin D1 in concentration- and time- dependent manners. Garcinone D also increased the protein levels of nuclear factor erythroid 2-related factor (Nrf2) and heme oxygenase-1 (HO-1) in concentration- and time- dependent manners, and inhibiting Nrf2 activation by brusatol could partly reverse garcinone D-induced C17.2 cell proliferation. Taken together, it is the first time to show that garcinone D promotes the proliferation of C17.2 neural stem cells, which may involve the STAT3/Cyclin D1 pathway and Nrf2/HO-1 pathway. It would provide new inspiration to develop garcinone D as a lead compound to promote the proliferation of endogenous neural stem cells (NSCs).

1. Introduction

Neural stem cells (NSCs) can be simply defined as the cells with self-renewal and multi-directional differentiation potential, which can generate neurons, astrocytes and oligodendrocytes by asymmetric cell division [1]. Recent landmark studies have demonstrated the importance of NSCs as the therapeutic potential of various indications, such as impaired neurogenesis in aging brain, spinal cord injury and traumatic brain injury [2–4]. However, the application of NSCs transplantation is limited by ethical pressure, reliable sources, immunological rejection and others [5]. An alternative strategy for stem cell-based therapies to repair or restore the function of lesioned brain is to enhance or protect endogenous neurogenesis by factors or chemical compounds [6]. Granulocyte colony stimulating factor, AMD3100 (CXCR4 antagonist) and stromal cell-derived factor-1α synergistically improves memory and

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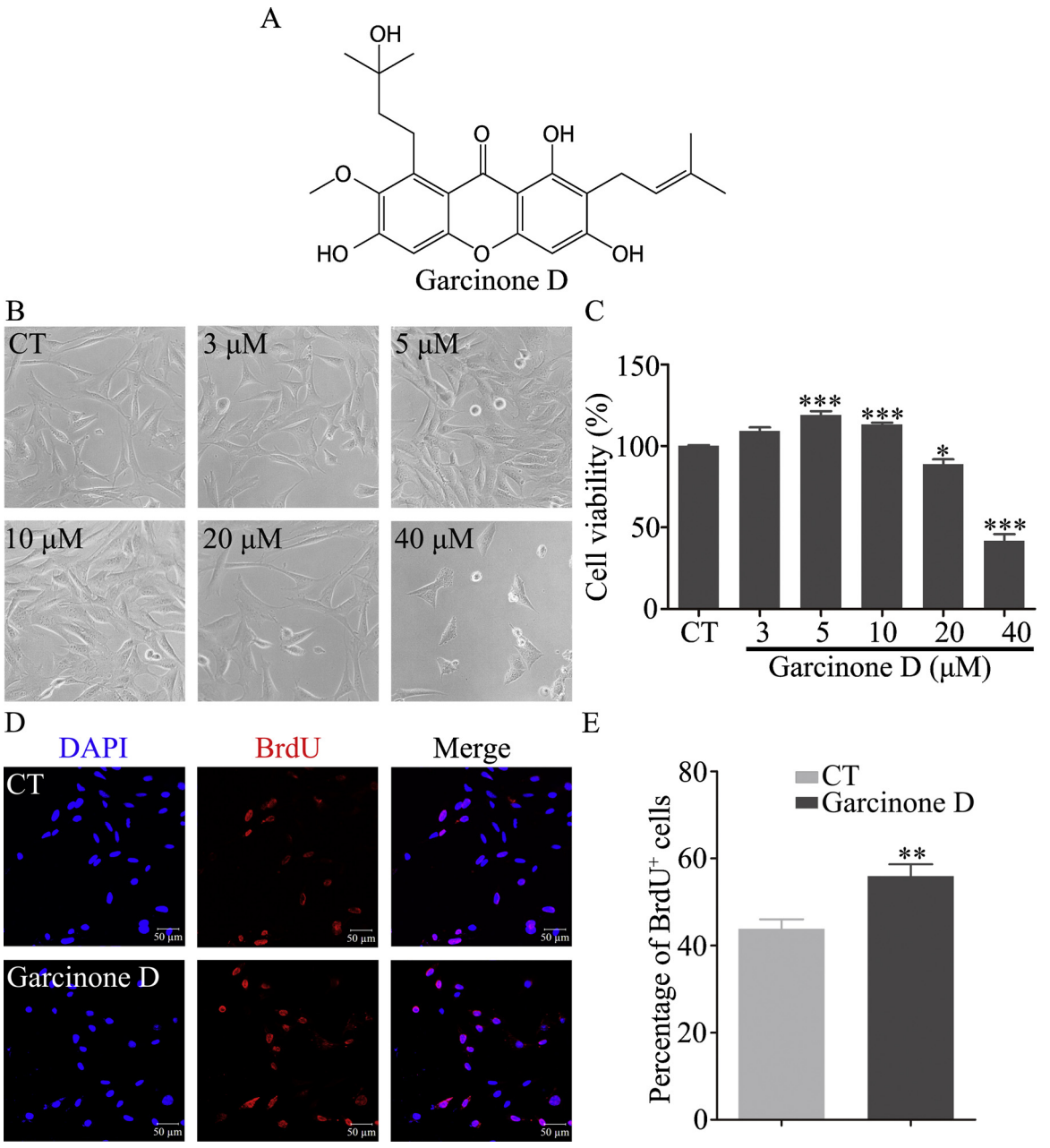

Fig. 1. Garcinone D promotes the proliferation of C17.2 neural stem cell. (A) Chemical structure of garcinone D. (B, C) C17.2 cells were exposed to the indicated concentrations of garcinone D for 24 h, then (B) cells were photographed using a photomicroscope (200 ×) and (C) cell viability was determined using MTT colorimetric assay, n = 6. * $P < 0.05$, *** $P < 0.001$ versus the control group. (D, E) After treatment with 5 μM garcinone D for 24 h, proliferated C17.2 cells were incubated in the presence of 10 μM BrdU for 4 h and then immunostained. (D) Representative images of costaining of DAPI (blue) and BrdU (red) were shown, and (E) the percentages of BrdU positive cells from 20 replicate images of control group and 5 μM garcinone D group were evaluated. ** $P < 0.01$ versus the control group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increases hippocampal neurogenesis in APP/PS1 double transgenic mice [7]. Flaubert et al. reported that EGb 761, a standardized *Ginkgo biloba* extract, enhances cell proliferation in the hippocampus of both young and old double transgenic mouse model (TgAPP/PS1) [8]. Therefore, it has been a new research hotspot to find small-molecule compounds that can activate endogenous stem cells.

Garcinia mangostana Linn (mangosteen) is a widespread tropical tree and native to Southeast Asia. Studies have shown that extracts of mangosteen pericarp have many biological functions, such as anti-oxidation, anti-inflammation, anti-microbial and so on [9–14]. Mangosteen pericarp diet exerts neuroprotective, anti-oxidative and anti-inflammatory effects and attenuates the deficit in spatial memory retrieval in triple transgenic Alzheimer's mice [15]. 30-day ingestion of a mangosteen-rich energy drink significantly increases anti-oxidant capacity and possesses anti-inflammatory benefits with no side effects on human hepatic and kidney functions [16]. However, there are few reports regarding the effects of garcinone D (Fig. 1A), a xanthone derivate isolated from mangosteen. In our preliminary experiments, we found that garcinone D treatment significantly increased the cell viability of HT22 murine hippocampal neuronal cells at the concentration of 30 μM [17]. For this reason, it will make more sense for us to investigate whether garcinone D could promote the proliferation of C17.2 cells, a clonal multipotent progenitor cell line originally derived from the external germinal layer of neonatal murine cerebellum [18,19]. As a result, we found