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Research article

Matrix metalloproteinase-13 downregulation and potential cartilage protective action of the Korean Red Ginseng preparation

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ABSTRACT

Background: The present study was designed to prepare and find the optimum active preparation or fraction from Korea Red Ginseng inhibiting matrix metalloproteinase-13 (MMP-13) expression, because MMP-13 is a pivotal enzyme to degrade the collagen matrix of the joint cartilage.
Methods: From total red ginseng ethanol extract, *n*-BuOH fraction (total ginsenoside-enriched fraction), ginsenoside diol-type-enriched fraction (GDF), and ginsenoside triol-type-enriched fraction (GTF) were prepared, and ginsenoside diol type-/F4-enriched fraction (GDF/F4) was obtained from *Panax ginseng* leaf extract.
Results: The *n*-BuOH fraction, GDF, and GDF/F4 clearly inhibited MMP-13 expression compared to interleukin-1β-treated SW1353 cells (human chondrosarcoma), whereas the total extract and ginsenoside diol-type-enriched fraction did not. In particular, GDF/F4, the most effective inhibitor, blocked the activation of p38 mitogen-activated protein kinase (p38 MAPK), c-Jun-activated protein kinase (JNK), and signal transducer and activator of transcription-1/2 (STAT-1/2) among the signal transcription pathways involved. Further, GDF/F4 also inhibited the glycosaminoglycan release from interleukin-1α-treated rabbit cartilage culture (30.6% inhibition at 30 μg/mL).
Conclusion: Some preparations from Korean Red Ginseng and ginseng leaves, particularly GDF/F4, may possess the protective activity against cartilage degradation in joint disorders, and may have potential as new therapeutic agents.

1. Introduction

The extracellular matrix (ECM) provides tension and strength in human articular cartilage. ECM consists of mainly collageneous materials and aggrecans [1], which are maintained under the control of a normal turnover process between new ECM synthesis by residing chondrocytes and breakdown by matrix metalloproteinases (MMPs) and aggrecanases. In certain pathological conditions, such as osteoarthritis, however, some MMPs are highly induced and degrade ECM. Among the MMPs, MMP-13 is the most important collagenase to degrade and destabilize ECM in human articular cartilages [2–4]. In this regard, it is thought that MMP-13 inhibitor(s) and/or downregulator(s) may play a beneficial therapeutic role of chondroprotection.

Korean Red Ginseng (steamed white ginseng, *Panax ginseng* Meyer) is famous for possessing various biological effects, including enhancing vital energy, enhancing immune capacity, and inhibition of cancer cell growth. Its major constituents are various ginsenosides that have been reported to exhibit numerous pharmacological activities, including vitality enhancement, immune modulation, and anticancer activity [5–7]. However, few investigations or few clinical studies of ginsenosides on cartilage degradation disorders have been reported.

Among the ginsenosides from Korean Red Ginseng, some are not present in white ginseng products [8,9]. Examples are ginsenoside Rg3, Rg5, Rk1, and F4 that are only detected in red ginseng extract. Previously, one ginsenoside, Rg3, was found to inhibit MMP-13 expression in human osteoarthritic chondrocytes [10]. We have

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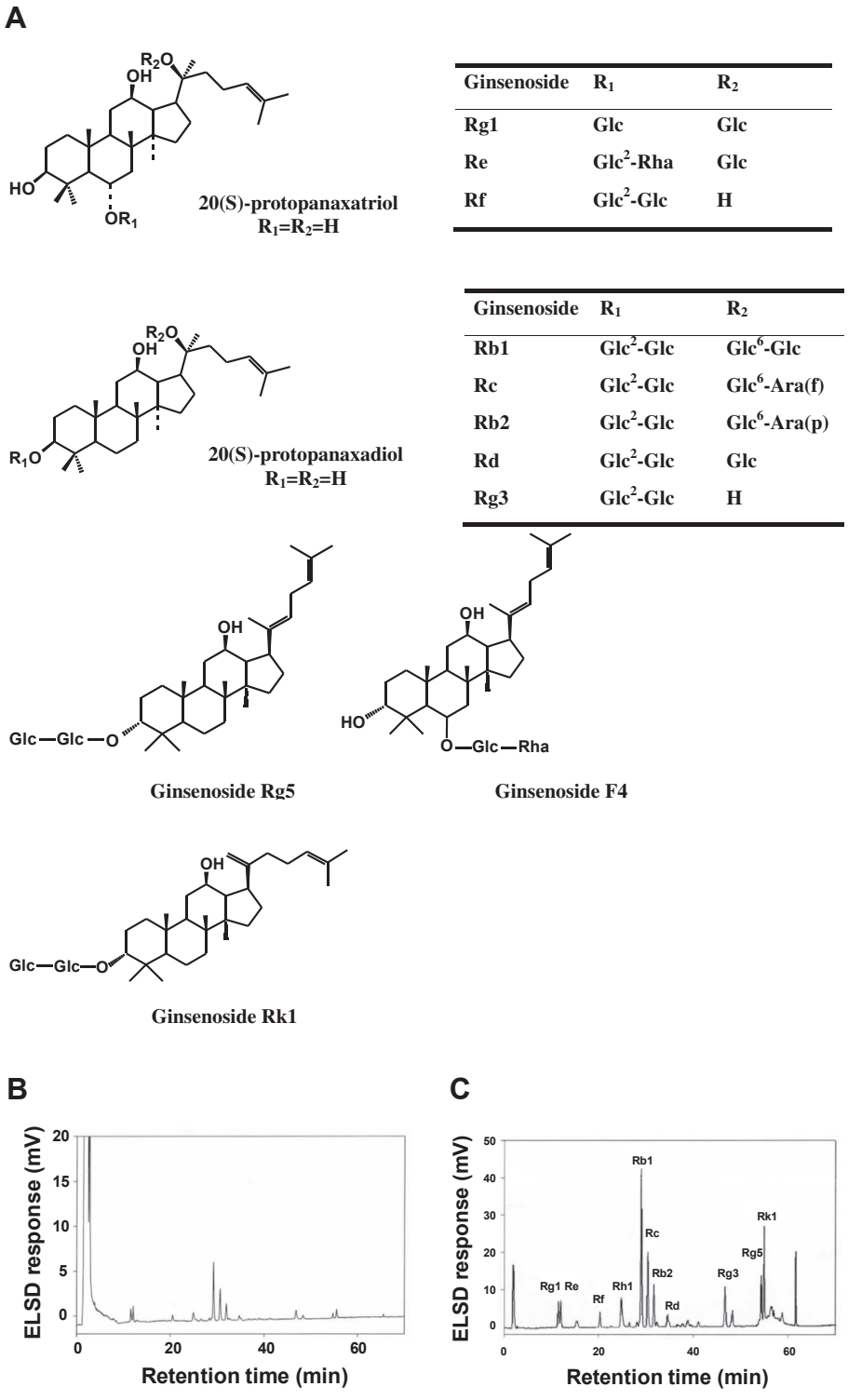

Ginsenoside	R_1	R_2
Rg1	Glc	Glc
Re	Glc^2-Rha	Glc
Rf	Glc^2-Glc	H

Ginsenoside	R_1	R_2
Rb1	Glc^2-Glc	Glc^6-Glc
Rc	Glc^2-Glc	Glc^6-Ara(f)
Rb2	Glc^2-Glc	Glc^6-Ara(p)
Rd	Glc^2-Glc	Glc
Rg3	Glc^2-Glc	H

Fig. 1. The chemical structures of ginsenosides and representative high-performance liquid chromatograms (HPLC) of the preparations from Korean Red Ginseng and ginseng leaves used in this study. (A) Chemical structures of ginsenosides. (B) HPLC of Korean Red Ginseng total extract. (C) HPLC of *n*-butanol fraction. The retention time and % of the area of each ginsenoside were: 11.43 min and 4.19% for Rg1; 11.90 min and 6.47% for Re; 20.27 min and 2.33% for Rf; 24.67 min and 7.73% for Rh1; 28.93 min and 30.89% for Rb1; 30.30 min and 16.24% for Rb2; 31.63 min and 7.89% for Rc; 34.43 min and 3.37% for Rd;46.40 min and 7.07% for Rg3(S); 47.93 min and 3.22% for Rg3(R); 54.30 min and 1.52% for Rk1; and 54.90 min and 2.47% for Rg5. (D) HPLC of ginsenoside diol-type-enriched fraction. (E) HPLC of ginsenoside diol-type-enriched fraction (GDF). (F) HPLC of GDF/F4. Note: Compared to GDF, GDF/F4 contains more hydrophobic ginsenosides such as F4, Rg3, and Rg5. ELSD stands for evaporative light scattering detection.

recently found that certain ginsenosides including Rc, Rd, Rf, F4, Rg1, and Rg3 inhibit MMP-13 induction from human chondrocytes, and some also block glycosaminoglycan (GAG) release from interleukin (IL)-1α-treated cartilage culture to some degree [11]. These previous findings strongly suggest that the Korean Red Ginseng products and/or some ginsenoside-enriched preparations may possess a significant inhibitory activity of MMP-13 expression and thereby block cartilage degradation. Thus, several ginseng