This study was aimed to examine the antiapoptotic effect of *Ulmus davidiana* extracts through regulation of the intracellular cation mobilization in U937 human monocytic cells. To investigate the modulatory effects on lipopolysaccharide-induced apoptosis and the Ca\(^{2+}\) signaling pathway, we measured the levels of intracellular Ca\(^{2+}\) and various protein markers such as Bax, Bcl-2, and PARP. To isolate biopotent molecules, the branches of *U. davidiana* were processed sequentially using 60% ethanol, supercritical fluid extraction, and ethyl acetate extraction of the remaining samples to obtain single fractions and catechin-glycoside, which is one of the known bioeffector molecules of *U. davidiana*. Lipopolysaccharide increased intracellular Ca\(^{2+}\) mobilization in U937 cells by inducing transient oscillations and markedly increased Bax and PARP protein expression and decreased Bcl-2 expression. All *U. davidiana* and catechin-glycoside significantly reduced lipopolysaccharide-induced intracellular Ca\(^{2+}\) mobilization and downregulated apoptosis-related molecules. These results suggest that *U. davidiana* and catechin-glycoside may be useful for improving immune system function.

Keywords: *Ulmus davidiana* extract, supercritical fluid extraction, intracellular Ca\(^{2+}\) signaling, LPS-induced apoptosis, catechin-glycoside

**INTRODUCTION**

The branches of *Ulmus davidiana var. japonica* (ULDA) has been used as a traditional Korean medicine for the treatment of inflammatory disorders (Lee, 1966; Hong et al., 1990; Kim et al., 2010). Previous pharmacological studies have reported that ULDA possesses antioxidant, anti-angiogenic, anticancer, and neuroprotective effects (Kim et al., 2005; Si et al., 2013a).
Recently, ULDA has also been used as a functional food for supplementation of amino acids (Oh et al., 2006), oligosaccharides (Eom et al., 2006), and other unknown metabolites that are involved in many biochemical metabolic processes (Carrillo and Borthakur, 2021).

Many studies have confirmed that ULDA contains several useful ingredients (Shin et al., 2000; Eom et al., 2006; Oh et al., 2006; Lee and Lim, 2007); however, the composition of the extract varies depending on the extraction method. The beneficial effects of ULDA have been recognized worldwide, including Asia, Europe, the United States (Xiu, 1988), and Korea, but its underlying mechanism of action on innate immunity and metabolism is not clear.

Recent studies indicate that ULDA extracts have various ameliorative effects on acute inflammatory responses in rats (Lee et al., 2013a; 2013b; Si et al., 2013b; Park et al., 2020), osteopenia (Zhuang et al., 2016), and in vitro models (Kim et al., 2019). Moreover, the supercritical fluid of ULDA has anti-inflammatory, anti-angiogenic (Jung and Park, 2006; Si et al., 2009b), and anti-melanin effects (Jeon et al., 2020; Xiong et al., 2021a; Xiong et al., 2021b).

Lipopolysaccharide (LPS), an important molecule in the microbial challenge, exerts an effect on intracellular Ca^{2+} levels ([Ca^{2+}]_i), the release of cytokines, and upstream signaling pathways (Azenabor et al., 2009). Intracellular Ca^{2+}-dependent pathways mediated LPS-induced activation of transcriptional factors and iNOS expression in mouse J774 macrophages (Chen et al., 1998).

ADP-ribosyl cyclase(s) modulate concentration of [Ca^{2+}], by mobilizing intracellular Ca^{2+} stores or by Ca^{2+} influx through plasma membrane Ca^{2+} channels in various cells (Rah et al., 2007; Kim et al., 2009; Park et al., 2011). Ca^{2+} signaling modulation via ADP-ribose cyclase is involved in signal transduction, including cell growth, differentiation, and death (Kim et al., 1993; Mehta et al., 1996; Liu et al., 2022). In this study, we investigated whether pharmaceutical inhibition of Ca^{2+} could be effective in protecting cells against programmed cell death. To test this hypothesis, we compared Ca^{2+} signals and apoptosis markers such as Bcl-2, Bax, and PARP-1 in LPS and supercritical fluid-fractionated ULDA-treated LPS groups of U937 cells.

Therefore, this study was performed to investigate the effects of supercritical fluid-fractionated ULDA, including initial fractions of polyphenols, hydrophobic substances, and flavonoids, on innate immunity modulation and recovery of innate immune function in an in vitro model.

**MATERIALS AND METHODS**

**Extraction and Isolation of U. davidiana**

In this study, extraction equipment was used for supercritical fluid extraction of U. davidiana branch (with bark). U. davidiana branch (with bark) was purchased from the Yangnyeongsi Medicine Market (Seoul, Korea), and impurities were removed, cleaned, and shaded for use as experimental material. One hundred kilograms of Ulmus davidiana branch (with bark) was extracted once with 60% edible ethanol at room temperature. The extract was then concentrated by removing 60% edible ethanol under vacuum to yield a quantity of 4.62 kg (U60E) (Figure 1). The dried sample was pulverized by passing through a 200 mesh screen and maintained at a temperature of 50°C in the pulverization tank. When the temperature stabilized, U. davidiana branch (with bark) samples were kept under CO_{2} gas at an equilibrium pressure of 400 bar, which was maintained through a control valve controlled by a high-pressure pump. After reaching the set pressure, extraction was performed by injecting 100 L of ethanol (300 ml/min) for 333 min to the bottom of the extraction tank. The high-pressure pump was set at a specific pressure and temperature for 30 min to remove the residual ethanol in the sample, and the extraction was completed by flowing CO_{2} gas. As described above, after supercritical extraction of 100 kg of U. davidiana branch (with bark) with 60% alcohol at room temperature, the extract was filtered, concentrated under vacuum, and freeze-dried to obtain 4.81 kg of the final product (USCFR) (Jeon et al., 2020). The filtrate (USCFR, 1 kg) was fractionated with ethyl acetate, and the ethyl acetate extract was concentrated under vacuum and freeze-dried to obtain 4.81 kg of the final product (USCFREA) (Figure 2), which was dissolved in water and filtered through filter paper no. 20 (Hyundai Micro, Seoul, South Korea). Purification and isolation were performed by liquid column chromatography with TLC monitoring. In addition, 185 g of USCFREA on Disogel (300 g, 3 × 50 cm) with 30% methanol under isocratic conditions in a Prep-LC system (20 ml/min, 280 nm) yielded catechin 7-O-β-D-apiofuranoside (compound 1) (Figure 3).

**Cell Culture**

U937 cells were obtained from the American Type Culture Collection and maintained in complete RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% antibiotics. After at least 14 days of proliferation, U937 cells were used for in vitro experiments.

**Intracellular Ca^{2+} Measurement**

Intracellular Ca^{2+} mobilization was measured as previously described (Park et al., 2011). Cells were plated manually on poly-L-lysine-coated confocal dishes (#100350; SPL, Pochun, Korea) and loaded with 1 mM Fluo-4 AM (Molecular Probes, CA, United States) at 37°C for 30 min. After washing with Hanks’ balanced salt solution medium containing 0.1% bovine serum albumin, changes in fluorescence were determined at 488 nm.
excitation/530 nm emission using an air-cooled argon laser system with a TE-2000 inverted microscope (Nikon, Tokyo, Japan) equipped with a temperature-controlled metal stage (Tokai Hit Co., Ltd., Shizuoka-ken, Japan). The emitted fluorescence at 530 nm was measured using a photomultiplier, and time series were acquired with a frame interval of 4 s. For the calculation of \([\text{Ca}^{2+}]_i\), the method described by Tsien et al. (1982) was applied with \(K_d\) for Fluo-4 using the equation \([\text{Ca}^{2+}]_i = K_d (F - F_{\text{min}})/(F_{\text{max}} - F)\). Each tracing was calibrated for maximal intensity \((F_{\text{max}})\) by adding 8 mM ionomycin and for minimal intensity \((F_{\text{min}})\) by adding 50 mM ethylene glycol tetraacetic acid at the end of each measurement.

**Western Blot Analysis**

Cell protein extracts were prepared immediately before use as follows: cells were solubilized by mixing with ice-cold lysis buffer [20 mM HEPES (pH 7.2), 1% Triton X-100, 10% glycerol, 1 mM EDTA, 1 mM phenylmethylsulfonyl fluoride, 50 mM NaF, 1 mM Na3VO4, leupeptin (10 mg/ml), pepstatin (10 mg/ml), and aprotinin (10 mg/ml)] by repeated trituration using a micropipette. The samples were then incubated for 1 h at 4°C. The supernatants were obtained after centrifugation at 20,000 \(\times\) g for 10 min. The concentration of the extracted proteins in the supernatant was determined by the Bradford assay using bovine serum albumin as a standard protein. Equivalent micrograms of proteins per lane were resolved on 7–12% SDS-polyacrylamide gel and electrotransferred to a polyvinylidene difluoride membrane (GE Healthcare). Antibodies against Bax, Bcl-2, PARP, and actin were used. Horseradish peroxidase-conjugated secondary antibodies (Santa Cruz Biotechnology) were used and visualized using
enhanced chemiluminescence (ECL). All immunoreactive signals were analyzed using densitometric scanning (LAS4000; GE Healthcare, United States).

Quantitative Chromatographic Analysis of U. davidiana Branch (With Bark)

HPLC analysis was conducted using a Waters 2,695 Separation Module (Waters Co., Milford, MA, United States) with a vacuum degasser, a binary pump, a 2,487 dual λ absorbance detector, a column compartment, and Empower software for data acquisition and integration. HPLC-grade reagents (J.T. Baker Co., Ltd., United States) were used for HPLC analysis (Si et al., 2008b, 2009a; An et al., 2019; Liu et al., 2021f). All solvents were filtered and degassed prior to use. The branches (with bark) of U. davidiana were accurately weighed to 2 g and dissolved in 50 ml of methanol. Samples were ultrasonicated for 15 min and filtered through filter paper no. 20 (600 × 600 mm, HYUNDAI Micro, Korea). The filtrate was further filtered through a 0.45-μm syringe filter (PVDF, Gelman, United States). Catechin 7-O-β-D-apiofuranoside (1) was separated on a Phenomenex KJ0-4282 guard column and a SkyPakC18 column (5 μm C18 HPLC column, 5 μm, 250 × 4.6 mm; SK Chemical) with a linear gradient of [D.W.MeOH: P2HO4 (940:50:1)]: [MeOH:P2HO4 (990:1)] = 100:0 to 0:100 for 4.6 mm; SK Chemical) with a linear gradient of [D.W.MeOH: P2HO4 (940:50:1)]: [MeOH:P2HO4 (990:1)] = 100:0 to 0:100 for 30 min. The column temperature was maintained at room temperature, and the flow rate was maintained at 1.0 ml/min. The sample injection volume was 20 μL. Eluted samples were monitored at 280 nm, and compound 1 was eluted at 14.45 ± 0.14 min. Compound 1 was detected in U. davidiana extracts. For these experiments, compound 1, U60E, USCFR, and USCFREA were prepared at a concentration of 1 mg/ml in methanol; the stock solutions were then diluted to 1,000, 500, 250, 125, and 62.5 ppm.

Statistical Analysis

All data are expressed as the mean ± SEM. One-way analysis of variance followed by Tukey’s multiple range test was used to compare each group (Si et al., 2008a; Du et al., 2019, 2022; Li et al., 2019, 2020; Liu et al., 2020a). Student’s t-test was used for comparison between the groups. Statistical analyses were conducted using SPSS for Windows (version 10.0; Chicago, IL, United States), and data indicated with different superscript letters represent significant difference at p < .05.

RESULTS AND DISCUSSION

Identification of Single Compound and Function

Catechin 7-O-β-D-apiofuranoside (Figure 3) from the U60E [12.16 ± 0.15 μg/ml], USCFR [131.45 ± 0.18 ppm (μg/ml)], and USCFREA [350.98 ± 0.16 ppm (μg/ml)] fractions and the catechin-glycoside-rich fraction (Com.1 rich fraction) were determined using a calibration equation (y = 6,857.3x–42,331; R² = 0.9985) (Figures 2, 3) (Table 1 and Table 2). The chemical structure of purified compound 1 (Figure 3) was determined using ChemDraw (PerkinElmer, MA, United States).

Definition of Compounds

In this study, we established a methodology to produce a high-content extract (Com.1 rich fraction) having a content of Com.1 10–30 times higher than that in general alcohol extracts, which overcame the obstacle to developing pharmaceuticals or functional materials derived from natural products. We believe that this new method will be helpful in obtaining large quantities of active substances (Figure 4).

Regulation of Ca²⁺ Signal by ULDA Extracts and Catechin-Glycoside

We assessed whether LPS would increase intracellular Ca²⁺ mobilization in U937 cells, mimicking cell exposure to Gram-negative bacteria, and whether ULDA extracts and catechin-glycoside could protect cells from LPS exposure (Figure 5). Intracellular Ca²⁺ mobilization in LPS-treated U937 cells was monitored by confocal microscopy. We observed that LPS at micromolar concentration induced transient Ca²⁺ oscillations with medium amplitude in U937 cells (Figures 5B,E,H,K). Therefore, we determined whether ULDA extracts and catechin-glycoside (each 50 μg/ml) reduced Ca²⁺ mobilization in response to LPS treatment (Figures 5C,F,I,L). All types of ULDA extracts (U60E: Figures 5A–C panels; USCFR: Figures 5D–F panels; USCFREA: Figures 5G–I panels) and catechin-glycoside (Figures 5J–L panels) reduced LPS-induced Ca²⁺ mobilization within a few minutes of pretreatment. These results suggest that LPS induces Ca²⁺ mobilization and that ULDA extracts and catechin-glycoside can reduce LPS-induced damage signals in U937 cells.

TABLE 1 | Retention time of compound 1 from Ulmus davidiana branch (with bark).

| Material       | Retention time (min) |
|----------------|----------------------|
| Standard       | 14.449 ± 0.14        |
| U60E           | 14.271 ± 0.12        |
| USCFR          | 14.482 ± 0.16        |
| USCFREA        | 14.687 ± 0.15        |

The results are expressed as the mean ± S.D. (n = 3).

TABLE 2 | Concentration of compound 1 from Ulmus davidiana branch (with bark).

| Material | Concentration (μg/ml) |
|----------|-----------------------|
| U60E     | 12.16 ± 0.15          |
| USCFR    | 131.45 ± 0.18         |
| USCFREA  | 350.98 ± 0.16         |

The results are expressed as the mean ± S.D. (n = 3).
FIGURE 4 | Representative HPLC chromatograms of (A) compound standard, (B) U60E [branch (with bark) 60% pre-ethanol A extract], (C) USCFR [branch (with bark) supercritical extraction residue 60% edible ethanolic extract from U. davidiana], (D) USCFREA [ethyl acetate layer extract of USCFR], and (E) catechin-glycoside–rich fraction. U60E = 1,000 ppm, USCFREA = 1,000 ppm, USCFR = 1,000 ppm, and catechin-glycoside–rich fraction = 1,000 ppm.
Antiapoptotic Effects on U937 Cells

Next, we examined apoptotic signaling response in U937 cells treated with 1 μg/ml LPS (Figures 6A–D). Administration of LPS increased the expression of apoptosis markers such as Bax and PARP and reduced the expression of Bcl-2, an antiapoptotic protein. Pretreatment with ULDA extracts (Figures 6A–C) and catechin-glycoside (Figure 6D) markedly reversed Bax and PARP protein expression levels; moreover, Bcl-2 expression was significantly elevated in a dose-dependent manner. Future comprehensive experimental studies might improve our understanding of other molecular pathways activated by ULDA extracts and catechin-glycosides in various disease-related signaling processes and help guide prospective clinical studies evaluating their effects and appropriate usage.

Lipopolysaccharide is a major virulence factor, and previous studies have demonstrated that LPS induces apoptosis in the murine macrophage-like cell line J774.1 (Suzuki et al., 2008; Ude et al., 2020), but not in humans. In this study, we emphasized the important role of the nuclear apoptotic pathway leading to Bax and PARP activation in LPS-induced apoptosis of human macrophages, U937 cells, and suggested that catechin-glycoside is a good candidate for amelioration of inflammatory disorders. However, when using natural materials with excellent physiological activity, it is necessary
to review and consider the optimal process for biological manufacturing.

Intracellular Ca\textsuperscript{2+} mobilization is a universal signaling pathway in which cells respond to a wide range of external stimuli such as hormones, chemicals, and other organic/inorganic compounds (Lee and Zhao, 2019; Dara et al., 2021). Stimulation of Ca\textsuperscript{2+} mobilization is initiated by the activation of second messenger production in the cytosol, which activates Ca\textsuperscript{2+} release from stores, such as the endoplasmic reticulum and endolysosomes (Streb et al., 1983). Ca\textsuperscript{2+} influx played an important role in the [Ca\textsuperscript{2+}]i mobilization pathway in U937 cells and well-defined LPS-induced cytokine production (Wehrhahn et al., 2010) via the transient receptor potential melastatin 2 (TRPM2) pathway. In addition, LPS-induced U937 apoptotic signaling is mediated by the transient receptor potential vanilloid subtype 1 (TRPV1) channel along with the cytosolic ROS signaling pathways (Güzel and Akpınar, 2021). These LPS-induced apoptotic signals are dependent upon mitochondrial dysfunction (Kuwabara and Imajoh-Ohmi, 2004), which is expected to be a parallel mechanism. In this study, we observed the effect of [Ca\textsuperscript{2+}]i mobilization on LPS-induced cell apoptosis and inhibitory effects of ULDA extract fractions and catechin-glycoside in U937 cells, but the critical pathway was not defined clearly and needs to be further investigated.

In many similar studies, an optimal extraction method was developed to obtain large quantities of effective substances from the same amount of natural raw materials while considering cost, space, facilities, and infrastructure (Liu et al., 2017; Hu et al., 2018; Lu et al., 2019; Kumar et al., 2020; Wang et al., 2020; Xu et al., 2020c; Yang et al., 2020; Ha et al., 2021; Huang et al., 2021; Zheng et al., 2021). Accordingly, the most commonly used extraction methods in academia and industry include hot water extraction, ethanol extraction, ultrasonic extraction, pressurized extraction, and supercritical extraction (Si et al., 2011; Chen et al., 2016; Hu et al., 2017; Xie et al., 2018, 2019; Yang et al., 2019; Xu et al., 2020a, Xu et al., 2020b, Xu et al., 2021a, Xu et al., 2021b; Wang et al., 2021a; Liu et al., 2021a, 2021b, 2021c). Each extraction method has its advantages and disadvantages that should be considered in many ways at the laboratory level and future commercialization level (Dai et al., 2020a; Liu et al., 2020b; Liu et al., 2021d; Liu et al., 2021e; Dai et al., 2020b; Chen et al., 2020; Chen et al., 2021; Ma et al., 2021; Zhang et al., 2021). Among various extraction methods, supercritical extraction technology has the advantages of being eco-friendly, use of safe organic solvents, and avoidance of environmental pollution. Thus, we used supercritical extraction technology for obtaining *U. davidiana* extracts with low cytotoxicity (Mun et al., 2018; Seo et al., 2018). Traditionally, water and alcohols (methanol or ethanol) have been used for the extraction of basic ingredients in local and industrial fields, but the risks and advantages of nonspecific classification between molecules exist (Cho et al., 2017). Therefore, fractionation with various solvents following polarity, ionic strength, hydrophilicity, and hydrophobicity along with purification has been performed worldwide, and techniques for the synthesis of the same molecules have been developed (Rho et al., 2004; Nan et al., 2013; Ravichandiran et al., 2019; Fang et al., 2020; Wang et al., 2021b). In this study, we extracted effective molecules from the residual material by supercritical fluidic extraction (Mun et al., 2018; Seo et al., 2018). Considering that these residues could retain relatively

![Figure 6](https://example.com/figure6.png)
hydrophilic molecules after supercritical fluid extraction, we performed common hydrophilic and hydrophobic extraction methods using 60% edible ethanol and ethyl acetate, respectively.

In this study, to examine the value of the supercritical extraction residue, physiological activity study was performed by extracting the supercritical extract of *U. davidiana* using 60% alcohol. In addition, ethyl acetate solvent analysis was conducted as a part of the production method to examine the added physiological value of *U. davidiana* supercritical extract and to verify the possibility of *U. davidiana* supercritical extraction residue as a new natural material.

**CONCLUSION**

The branches of *Ulmus davidiana* var. *japonica* (ULDA) has traditionally been used in Korea and other Asian countries. ULDA extracts are complex substances consisting of many components; a few of them have pharmaceutical applications in various diseases, such as inflammation and other chronic problems, and as antimicrobial agents.

In this study, we investigated the effects of supercritical fluid-fractionated ULDA, including initial fractions of polyphenols, hydrophobic substances, and flavonoids, on innate immunity modulation and recovery of innate immune function in an *in vitro* model. Future experiments are needed to investigate the beneficial effects of these resources in other diseases using *in vivo* models.

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**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

**AUTHOR CONTRIBUTIONS**

Investigation, J-HY, YM, and H-OK; Supervision, CS, K-HP, and S-EC; Writing—original draft, S-EC and K-HP; Writing—review and editing, CS and J-HJ.

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