ORIGINAL ARTICLE

Momordica charantia extracts obtained by ultrasound-assisted extraction inhibit the inflammatory pathways

Ha-Rim Kim[1] · Eun-Mi Noh[1] · Seung-Hyeon Lee[1] · Saerom Lee[2] · Dong Hee Kim[2] · Nam Hyouck Lee[2] · Seon-Young Kim[1] · Mi Hee Park[1]

Abstract

Background *Momordica charantia* is a member of the *Cucurbitaceae* family and has traditionally been used for medical nutritional therapy to cure diabetes, and its various biological properties have been reported. However, several studies have demonstrated that *M. charantia* may exert toxic or adverse effects under different conditions. In this study, we prepared an *M. charantia* extract using ultrasound-assisted extraction, which is a green technology, and verified its anti-inflammatory effects.
Objectives The aim of this study was to investigate the anti-inflammatory effects of *M. charantia* extract using ultrasound-assisted extraction in LPS-induced Raw264.7 macrophages and explore the potential mechanism mediated by the MAPK/NF-κB signaling pathway.
Results We found that the *M. charantia* extract was non-toxic up to a concentration of 500 µg/mL in Raw264.7 cells. We verified that treatment with *M. charantia* extract significantly reduced the production of nitric oxide and proinflammatory cytokines, including TNF-α, IL-1β, IL-2, and IL-6, in LPS-stimulated RAW264.7 cells. Moreover, the anti-inflammatory cytokine IL-10 was dramatically increased by treatment with the *M. charantia* extract. In addition, the phosphorylation of the transcription factor NF-κB, which modulates the production of inflammatory proteins, including JNK, ERK, and p38, was reduced by downregulation of the MAPK signaling pathway.
Conclusion These results indicate that the *M. charantia* extract collected using an industrial ultrasonic system is non-toxic and has an anti-inflammatory effect through regulation of the NF-κB and MAPK pathways, suggesting that it can act as a therapeutic candidate for the treatment of inflammatory diseases.

Keywords *M. charantia* · Ultrasound-assisted extraction · MAPK · NF-κB · Cytokines · Macrophages

Introduction

Cucurbitaceae has traditionally been used for medical nutritional therapy and medicine in many areas (Sur et al. 2020). Bioactive compounds, including flavonoids, phenols, terpenoids, saponins, sterols, and glycosides, have been isolated from the fruits, leaves, and seeds of *M. charantia* (Jia et al. 2017). The fruits and leaves of Momordica species are rich in phytochemicals and have nutritional and nutraceutical ingredients, which may have multiple health-promoting effects. Various biological properties of *M. charantia* have been reported, such as antioxidant, antidiabetic, anticancer, neuroprotective, antihyperglycaemic, antibacterial, antiviral, anthelmintic, antiulcer, antilipolytic, hepatoprotective, and immunomodulatory activities (Çiçek 2022; Liu et al. 2021).

For use as functional materials, raw materials must be subjected to an extraction process. There is a continuous demand for the development of alternative eco-friendly methods to improve the use of organic solvents with a risk of toxicity and environmental pollution (Nipornram et al. 2018). Since the development of sustainable green technology in 1991, research has been conducted to reduce or eliminate the use of chemicals and solvents that are harmful to human health and the environment. Examples of these green technologies include ultrasound-assisted extraction,

✉ Seon-Young Kim
seon02@jami.re.kr

✉ Mi Hee Park
mhpark@jami.re.kr

1 Jeonju AgroBio-Materials Institute, Jeonju-si 54810, Republic of Korea

2 3FC Co., In KFRI, 245, Wanju-gun 55365, Republic of Korea

microwave-assisted extraction, accelerated solvent extraction, and supercritical liquid extraction (Flórez-Fernández et al. 2019; Choi et al. 2020). Among them, ultrasound-assisted extraction is useful for obtaining high-quality extracts with high yield. Ultrasonic-assisted solvent extraction of plant secondary metabolites has been widely used in the fields of food, chemistry, and medicine (Flórez-Fernández et al. 2019). Ultrasound treatment on the medium generates air bubbles, which cause cavitation. When a cavitation bubble collapses near the cell wall, it exerts a strong impact on the surface to destroy the cell wall, allowing the solvent to enter the cell effectively, thus facilitating extraction (Choi et al. 2020). It is a green extraction technique with a high extraction rate, low energy consumption, and short extraction cycle (Wu et al. 2022). It has been found that ultrasound-assisted extraction significantly increased the extraction rate of flavonoids at low ethanol levels, low temperatures, and shorter time periods while increasing the antioxidant activity of the flavonoids by 76%, achieving a more environmentally friendly and less time-consuming method than traditional solvents (Egüés et al. 2021; Wu et al. 2022). Therefore, in this study, we obtained an *M. charantia* extract using an ultrasound system and verified its biological properties, especially its anti-inflammatory effects.

Inflammatory diseases are caused by dysregulated inflammation. Normally, the inflammatory response maintains an equilibrium between anti-inflammatory and proinflammatory cytokines. The excessive production of proinflammatory mediators plays a role in the progression of chronic inflammatory-related diseases, including metabolic syndromes, atherosclerosis, inflammatory bowel diseases, dermatitis, and cancers (Serhan et al. 2018; Herrero-Cervera et al. 2022; Bhosale et al. 2022). Therefore, controlling inflammation is very important for the prevention and treatment of diseases. Inflammatory signals are transferred indirectly or directly depending on the particular cell type. Macrophages play important roles in inflammation and can be activated by endotoxin, which causes the production of inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6), releasing inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and catalyzing the production of nitric oxide (NO) as an inflammatory mediator (Jin et al. 2022; Watanabe et al. 2019). Macrophages are important immune cells and play a critical role during inflammation in host defences against pathogen infection. Therefore, lipopolysaccharide (LPS)-induced inflammation in RAW264.7 murine macrophages is a widely used inflammation model. The stimulated cells exhibit typical inflammatory responses by producing NO and reactive oxygen species (ROS) and generating proinflammatory mediators such as IL-6, TNF-α, and iNOS. Several signaling pathways were demonstrated to be closely associated with inflammation in LPS-induced RAW264.7 cells. The transcriptional regulator nuclear factor-kB (NF-κB) is vitally involved in the pathogenesis of various inflammatory diseases and modulates the production of many cytokines and mediators (Liu et al. 2017). Furthermore, NF-κB can be activated via mitogen-activated protein kinases (MAPKs), such as c-Jun NH$_2$-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38, which are regulated by mitogen-activated protein kinase (MEK) (Hoesel et al. 2013). It has been reported that various natural compounds derived from medicinal plants are effective in the treatment of inflammatory diseases through regulation of the related signaling pathways (Jayakumar et al. 2021; Chauhan et al. 2022).

Therefore, the objectives of this study were to verify the *M. charantia* extract by an ultrasound system, which is a green technology, for its anti-inflammatory effects and to further determine the possibility of using the *M. charantia* extract to treat inflammatory diseases.

Materials and methods

Preparation of *M. charantia* extract

M. charantia (bitter melon) was purchased from the Jeongeup Agriculture Cooperative in Korea. The bitter melon was washed thoroughly with running water, sliced, and dried at 50 °C for 24 h using a hot air dryer (HKT 300; Narotech Co., Naju, Korea). The dried bitter melon was prepared as a powder using a grinder (DSMP-370; DukSan Co., Siheung, Korea) and was stored below 10 °C. Ultrasonic extracts of bitter melon were obtained by two methods, using distilled water and 60% ethanol. For extraction, each solvent was added to 40 times the weight of bitter melon powder and sonicated for 24 h under the conditions of 20 kHz frequency and 1,260 W amplitude. Each extract was filtered using a 0.5 μm filter and then freeze-dried.

Cell culture

The murine macrophage-like cell line RAW264.7 was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured as previously described (Kim et al. 2022). In brief, the cells were cultured in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen, Carlsbad, CA, USA) with 10% heat-inactivated fetal bovine serum (FBS) (Invitrogen, Carlsbad, CA, USA) and penicillin/streptomycin (100 U/mL) (Invitrogen, Carlsbad, CA, USA) at 37 °C under a humidified atmosphere containing 5% CO$_2$.

Cell viability assay

The cells were treated with *M. charantia* for 24 h, and cell viability was then estimated using an MTS assay. A 10 μL MTS solution was added to each well, and the cells were further incubated for an additional 4 h. The optical density was measured by a microplate reader (Multiskan Go, Thermo Scientific, Waltham, MA, USA) at 490 nm. The values of the control were considered 100% viable.

NO measurements

The cells were stimulated with or without LPS (1 μg/mL) (Sigma, St Louis, MO, USA) in the absence or presence of various concentrations of *M. charantia* extracts for 18 h. NO production in the culture medium was measured with a commercially available NO (nitric oxide) Plus Detection kit (iNtRON Biotechnology, Sungnam, Korea) based on the Griess method. The culture medium was mixed with Griess reagent (equal volumes of sulfanilamide in the reaction buffer and naphthylethylenediamine in the stabilizer reaction) and incubated for 20 min at room temperature. The concentration of nitrite was determined using the sodium nitrite ($NaNO_2$) standard curve at 540 nm with a microplate reader.

Cytokine assay

Cells were treated with different concentrations (100, 250, 500 μg/mL) of *M. charantia* extract at 37 °C for 18 h. Then cell culture medium was prepared and used to measure the cytokine concentration. TNF-α and IL-1β, IL-2 and IL-6 concentrations were measured by enzyme-linked immunosorbent assay (ELISA) kits provided by R&D Systems, Inc. (Abingdon, UK) according to the manufacturer's protocol.

Western blot analysis

Whole-cell lysates of the cultured cells were obtained and separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and Western blot analysis was performed as described previously (Kim et al. 2022). The primary and secondary antibodies used in Western blot analyses were purchased from Cell Signaling Technology Inc. (Beverly, MA, USA).

Statistical analysis

The data are expressed as the means ± SD, and all statistical analyses were performed with Sigmaplot v14.0 software (Systat Software Inc., San Jose, CA, USA). Statistical analysis was applied to identify the differences, followed by one-way analysis of variance (ANOVA) and Tukey's

honestly significant difference (HSD) post hoc tests. A value of $P < 0.05$ was considered significant.

Results

The effect of *M. charantia* extract on LPS-induced NO production in RAW264.7 cells

LPS-induced inflammation in mouse macrophages is a common model of inflammation used in in vitro anti-inflammatory studies (Qi et al. 2022). As a versatile mediator involved in a large number of pathological and physiological processes, NO is a proinflammatory molecule that plays an important role in the inflammatory response, and the amount of cytosolic NO secreted indirectly reflects the degree of inflammation that occurs. NO is an indicator of inflammation in several inflammatory diseases (Zamora et al. 2000). Thus, the effect of *M. charantia* extract on LPS-induced NO production in RAW264.7 cells was investigated by measuring the NO released into the culture medium by the Griess reaction. First, we set up the ultrasonic extraction conditions using ethanol and water as solvents. Ethanol and water extracts showed similar effects (data not shown). Therefore, we optimized the extraction time with water as a solvent (2, 4, and 24 h). As shown in Fig. 1, NO production was most effectively suppressed under the extraction conditions for 4 h. Treatment with LPS (1 μg/mL) significantly increased the NO level in RAW264.7 cells. LPS induces the production of various inflammatory factors, such as TNF-α, IL-1β, and IL-6 (Liu et al. 2018). Treatment of *M. charantia* extracts (100, 250, and 500 μg/ml) with LPS for 18 h significantly reduced the LPS-induced NO levels in
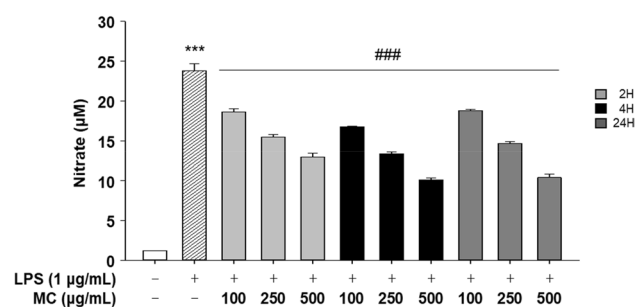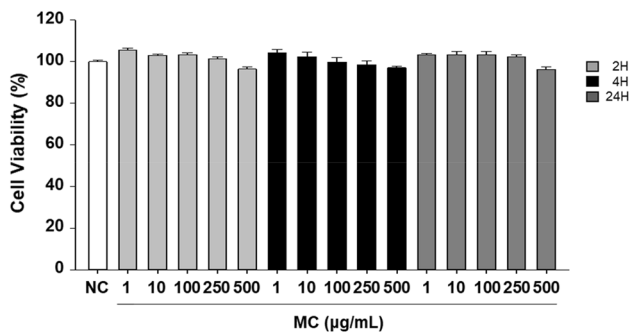

Fig. 1 The effect of *M. charantia* extract (MC) on LPS-induced NO release in RAW264.7 cells. Cells were treated with 1 μg/mL LPS alone or with LPS plus different concentrations (100, 250, 500 μg/mL) of MC at 37 °C for 18 h. NO levels were determined by the Griess reaction as described in the Methods section in supernatants from RAW264.7 cells. Values represent the means ± SD for three independent experiments performed in triplicate. *Indicates a significant difference from the non-treated control group (***$P < 0.001$). #Indicates a significant difference from the LPS-treated group (\#\#\#$P < 0.001$)

a concentration-dependent manner (Fig. 1). There was no cytotoxicity at the treatment concentration of *M. charantia* extract (Fig. 2).
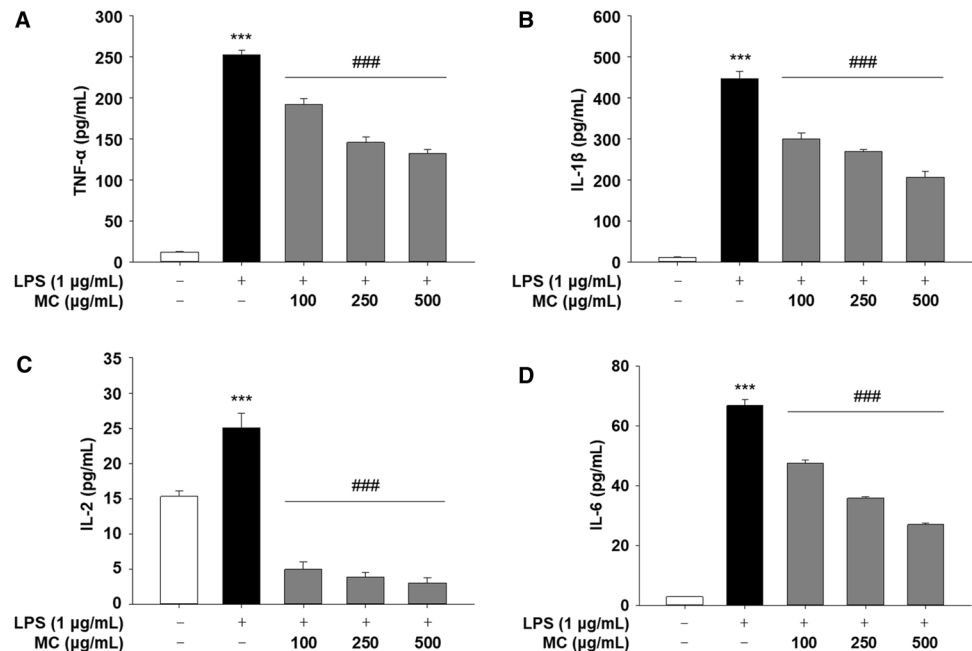
The effect of *M. charantia* on the release of proinflammatory cytokines

To determine whether *M. charantia* extract can modulate inflammatory cytokine induction by LPS in RAW264.7 cells, the levels of TNF-α, IL-1β, IL-2, and IL-6 were measured after treatment with *M. charantia* extract and LPS in RAW264.7 cells. LPS significantly increased the levels of TNF-α, IL-1β, IL-2, and IL-6, which were significantly reduced by *M. charantia* extract treatment. In addition, the *M. charantia* extract showed a concentration-dependent effect (Fig. 3A–D).

Fig. 2 The effect of *M. charantia* extract (MC) on cell viability. Cells were treated with different concentrations (100, 250, 500 μg/mL) of MC at 37 °C for 24 h. Cell viability was evaluated as described in the Methods

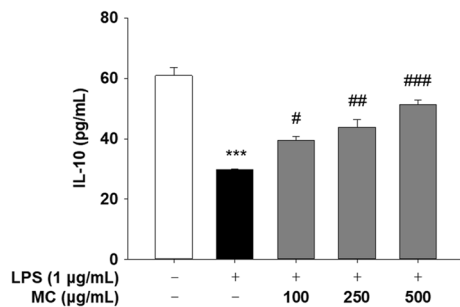## The effect of *M. charantia* on the release of anti-inflammatory cytokines

In addition to the above results, the level of IL-10 was measured after treatment with LPS and *M. charantia* extract in RAW264.7 cells to confirm whether *M. charantia* extract treatment can induce alterations in anti-inflammatory cytokines in RAW264.7 cells. As a result, the level of IL-10 markedly increased in the *M. charantia* extract-treated group compared to the LPS group (Fig. 4).

Involvement of the MAPK and NF-κB pathways in the inhibitory effect of *M. charantia* on LPS-induced inflammation

Cytokines such as TNF-α and IL-6 have been reported to trigger inflammation by activating key proteins in signaling pathways, such as NF-κB and MAPK. To further investigate the effects of *M. charantia* extract on inflammatory pathways, we investigated the NF-κB- and MAPK-related pathways. We observed that *M. charantia* extract inhibited the phosphorylation of IκB-α and NF-κB by LPS and suppressed the expression of COX-2 and iNOS (Fig. 5A). In addition, NF-κB could be activated through MAPK, and we verified that the phosphorylation of p38, pERK, and pJNK was reduced by *M. charantia* extract (Fig. 5B). From these results, we conclude that the *M. charantia* extract is effective against inflammation through downregulation of the NF-κB-regulated MAPK pathway and thereby inhibition of proinflammatory cytokine production and inflammatory proteins, as shown in Fig. 6.

Fig. 3 The effect of *M. charantia* extract (MC) on the release of proinflammatory cytokines. Cells were treated with different concentrations (100, 250, 500 μg/mL) of MC at 37 °C for 18 h. Then cell culture media was prepared and used to measure the cytokine concentration. TNF-α (**A**), IL-1β (**B**), IL-2 (**C**) and IL-6 (**D**) concentrations were quantified by ELISA. Data shown are the mean ± SD. *Indicates a significant difference from the non-treated control group (***$P < 0.001$). #Indicates a significant difference from the LPS-treated group (###$P < 0.001$)

Fig. 4 The effect of *M. charantia* extract (MC) on the release of anti-inflammatory cytokines. Cells were treated with different concentrations (100, 250, 500 μg/mL) of MC at 37 °C for 18 h. Then cell culture media was prepared and used to measure the cytokine concentration. The IL-10 concentration was quantified by ELISA. Data shown are the mean ± SD. *Indicates a significant difference from the non-treated control group (***$P < 0.001$). #Indicates a significant difference from the LPS-treated group (#$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$)
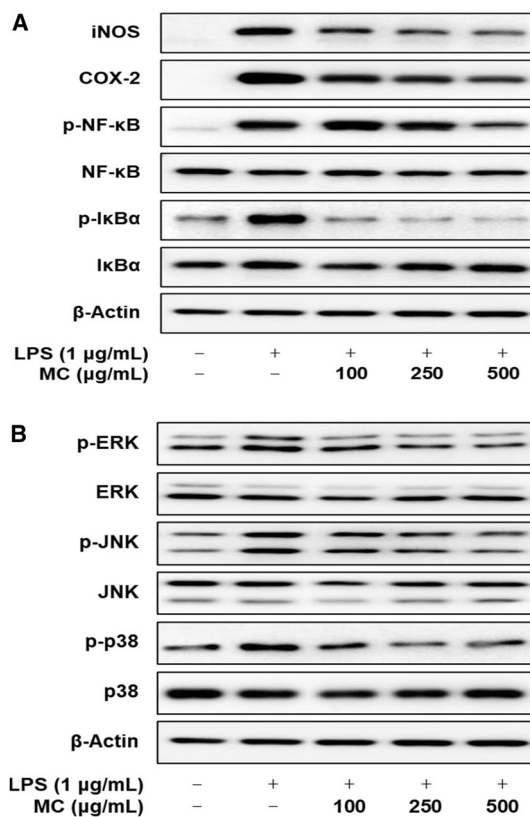

Fig. 5 Effect of *M. charantia* extract (MC) on the NF-κB and MAPK signaling pathways. Cells were treated with different concentrations (100, 250, 500 μg/mL) of MC at 37 °C for 18 h. Then cell lysates were prepared and used for western blotting. Protein expression of the (**A**) NF-κB and (**B**) MAPK signaling pathways was determined by Western blotting. Equal amounts of total protein were resolved by SDS–PAGE. β-Actin was employed as an internal reference

Discussion

This study was performed to evaluate the anti-inflammatory efficacy of *M. charantia* ultrasonic extract in RAW264.7 immune cell systems. Green technology has been developed to reduce or eliminate the use of chemicals and solvents harmful to the environment and human health. Therefore, it is necessary to develop materials using green technology for industrialization. In particular, ultrasound-assisted extraction is useful to obtain high-quality extracts with increased yields. In this study, we developed the extraction methods using an ultrasonic extraction system and then determined the pharmacological activities for anti-inflammatory uses. The results showed that the *M. charantia* extract was not cytotoxic. We showed that the *M. charantia* extract reduced NO production and the release of inflammatory cytokines. Moreover, the expression of proinflammatory proteins was decreased by *M. charantia* extract. Inflammatory proteins are regulated by the MAPK and NF-κB pathways. Several natural products from plant extracts regulate inflammatory proteins through regulation of the MAPK and NF-κB signaling pathways (Jayakumar et al. 2021; Chauhan et al. 2022).

In this study, we showed that the production of TNF-α was reduced by *M. charantia* extract. TNF-α is a proinflammatory cytokine that is involved in the pathogenesis of some inflammatory and autoimmune diseases (Jang et al. 2021). Physiologically, TNF-α is a crucial component for a normal immune response. TNF-α activates and regulates the immune system, but the inadequate or excessive production of TNF-α may be harmful and can lead to disease. Inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, and non-infectious uveitis are due to abnormal secretion of TNF-α; thus, TNF-α can be classified as a key factor in severe pathological development (Nicolela et al. 2020). Due to the involvement of TNF-α in the pathogenesis of autoimmune diseases, TNF-α inhibitors have been successfully developed and applied to the clinical treatment of autoimmune diseases such as RA and Crohn's disease (CD) (Zhang et al. 2020).

Moreover, we also found that IL-1β was decreased by treatment with the *M. charantia* extract. IL-1β is a myeloid-derived proinflammatory cytokine that modulates adaptive and innate immune responses against distinct pathogens. However, when produced in excess, IL-1β drives both complex common inflammatory diseases, such as atherosclerosis, RA, and gout, and monogenic inflammatory disorders (Broderick et al. 2022). Evidence also suggests that IL-1β is pathologically activated in neurodegenerative conditions, such as Parkinson's and Alzheimer's diseases (AD) (Mendiola et al. 2018). In addition, IL-2 is considered as an important proinflammatory factor because it not only promotes the expansion of T cells and enhances the ability of natural
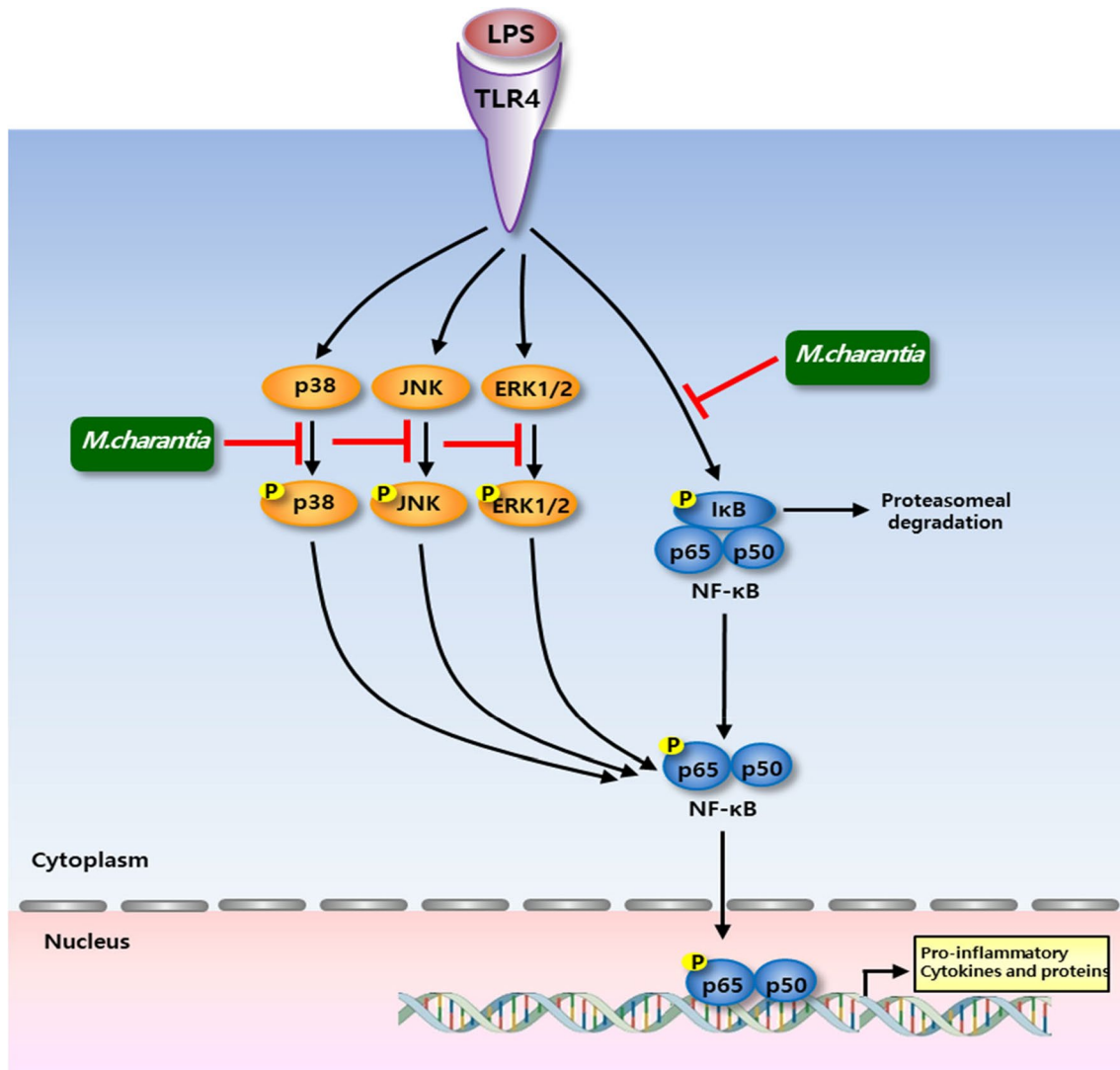
Fig. 6 Schematic diagram of the anti-inflammatory signaling activity of *M. charantia* extract

killer (NK) cells but also strengthens the body's anti-tumor immune response (Hu et al. 2019). Moreover, low-dose IL-2 has been used to treat systemic lupus erythematosus, type 1 diabetes, and other autoimmune diseases and has shown some efficacy (Graßhoff et al. 2021). We demonstrated that the dose of IL-2 was very low in the *M. charantia* extract-treated group, suggesting that it can be useful for the treatment of systemic lupus erythematosus, type 1 diabetes, and other autoimmune diseases. Additionally, secretion of IL-6 is also observed in atherosclerosis, Alzheimer's disease, systemic lupus erythematosus, multiple myeloma, RA, autoimmune deficiency disease, chronic inflammatory disease, and different types of cancer (Omoigui 2007). Interestingly, after viral infection, viral products also enhance the transcription or translation of IL-6 from cells such as fibroblasts, mesenchymal cells, endothelial cells, and many other cells. IL-10 is a major anti-inflammatory mediator that protects the host

from excessive responses to pathogens and microbiota and plays important roles in other environments, such as sterile wound healing, homeostasis, cancer, and autoimmunity (Saraiva et al. 2020). We found that *M. charantia* extract induces IL-10 production, suggesting that it could be used for anti-inflammatory diseases.

M. charantia has been approved by the Korean Ministry of Food and Drug Safety as a raw material to help suppress postprandial blood sugar rise. We compared the effects of *M. charantia* extracts using ethanol solvent and applied ultrasonic technology (data not shown). We found that the anti-inflammatory effect of *M. charantia* extract applied with ultrasonic technology was much higher than that of ethanol extraction. Further studies are needed to analyze the functional compounds of the *M. charantia* extract by ultrasonication. Compounds such as charantin, monordicin, cucurbitacin B, momordin, γ-aminobutyric acid, cryptoxanthin,

β-carotene, zeaxanthin, lycopene, lutein, and carotene have been studied as functional or index compounds of *M. charantia* (Cuong et al. 2021). Therefore, in future studies, we will demonstrate the efficacy evaluation for target diseases, including RA, IBD, and AD, and investigate the functional compounds.

Author contributions PMH and KHL wrote the paper and analyzed the data. KHL, KDH, LSR, LNH, NEM, and LSH contributed to performing the experiments and data analysis. KSY and PMH contributed to research planning.

Declarations

Conflict of interest Ha-Rim Kim declares that he has no conflict of interest. Eun-Mi Noh declares that she has no conflict of interest. Seung-Hyeon Lee declares that he has no conflict of interest. Saerom Lee declares that he has no conflict of interest. Dong Hee Kim declares that she has no conflict of interest. Nam Hyouck Lee declares that he has no conflict of interest. Seon-Young Kim declares that he has no conflict of interest. Mi Hee Park declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Bhosale PB et al (2022) Iridin abrogates LPS-induced inflammation in L6 skeletal muscle cells by inhibiting NF-κB and MAPK signaling pathway. Mol Cell Toxicol. https://doi.org/10.1007/s13273-022-00277-3

Broderick L, Hoffman HM (2022) IL-1 and autoinflammatory disease: biology, pathogenesis and therapeutic targeting. Nat Rev Rheumatol 18:448–463

Chauhan A et al (2022) Phytochemicals targeting NF-κB signaling: potential anti-cancer interventions. J Pharm Anal 12:394–405

Choi Y et al (2020) Development of an ultrasonic Doppler sensor-based swallowing monitoring and assessment system. Sensors (basel) 20(16):4529

Çiçek SS (2022) *Momordica charantia* L.-diabetes-related bioactivities, quality control, and safety considerations. Front Pharmacol 13:904643

Cuong DM et al (2021) Analysis of triterpenoids, carotenoids, and phenylpropanoids in the flowers, leaves, roots, and stems of white bitter melon (Cucurbitaceae, Momordica charantia). Trop J Pharm Res 20:155–160

Egüés I, Hernandez-Ramos F, Rivilla I, Labidi J (2021) Optimization of ultrasound assisted extraction of bioactive compounds from apple pomace. Molecules 26:3783

Flórez-Fernández N, Domínguez H, Torres MD (2019) A green approach for alginate extraction from *Sargassum muticum* brown seaweed using ultrasound-assisted technique. Int J Biol Macromol 124:451–459

Graßhoff H et al (2021) Low-dose IL-2 therapy in autoimmune and rheumatic diseases. Front Immunol 12:648408

Herrero-Cervera A, Soehnlein O, Kenne E (2022) Neutrophils in chronic inflammatory diseases. Cell Mol Immunol 19:177–191

Hoesel B, Schmid JA (2013) The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 12:86

Hu W et al (2019) Cancer immunotherapy based on natural killer cells: current progress and new opportunities. Front Immunol 10:1205

Jang DI et al (2021) The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. Int J Mol Sci 22:2719

Jayakumar T et al (2021) Targeting MAPK/NF-κB pathways in anti-inflammatory potential of rutaecarpine: impact on Src/FAK-mediated macrophage migration. Int J Mol Sci 23:92

Jia S, Shen M, Zhang F, Xie J (2017) Recent advances in *Momordica charantia*: functional components and biological activities. Int J Mol Sci 18:2555

Jin QH et al (2022) Anti-inflammatory effects of mesenchymal stem cell-conditioned media inhibited macrophages activation in vitro. Sci Rep 12:4754

Kim HR et al (2022) Comparison of laxative effects of fermented soybeans (*Cheonggukjang*) containing toxins and biogenic amines against loperamide-induced constipation mouse model. Nutr Res Pract 16:435–449

Liu T, Zhang L, Joo D, Sun SC (2017) NF-κB signaling in inflammation. Sig Transduct Target Ther 2:17023

Liu X et al (2018) LPS-induced proinflammatory cytokine expression in human airway epithelial cells and macrophages via NF-κB, STAT3 or AP-1 activation. Mol Med Rep 17:5484–5491

Liu Z et al (2021) The effect of *Momordica charantia* in the treatment of diabetes mellitus: a review. Evid Based Complement Alternat Med 2021:3796265

Mendiola AS, Cardona AE (2018) The IL-1β phenomena in neuroinflammatory diseases. J Neural Transm (vienna) 125:781–795

Nicolela Susanna F, Pavesio C (2020) A review of ocular adverse events of biological anti-TNF drugs. J Ophthal Inflamm Infect 10:11

Nipornram S, Tochampa W, Rattanatraiwong P, Singanusong R (2018) Optimization of low power ultrasound-assisted extraction of phenolic compounds from mandarin (*Citrus reticulata* Blanco cv. Sainampueng) peel. Food Chem 241:338–345

Omoigui S (2007) The Interleukin-6 inflammation pathway from cholesterol to aging–role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases. Immun Ageing 4:1

Qi Y, Duan G, Fan G, Peng N (2022) Effect of *Lycium barbarum* polysaccharides on cell signal transduction pathways. Biomed Pharmacother 147:112620

Saraiva M, Vieira P, O'Garra A (2020) Biology and therapeutic potential of interleukin-10. J Exp Med 217:e20190418

Serhan CN, Levy BD (2018) Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest 128:2657–2669

Sur S, Ray RB (2020) Bitter melon (*Momordica Charantia*), a nutraceutical approach for cancer prevention and therapy. Cancers (basel) 12:2064

Watanabe S, Alexander M, Misharin AV, Budinger GRS (2019) The role of macrophages in the resolution of inflammation. J Clin Invest 129:2619–2628

Wu EY et al (2022) Optimization of ultrasonic-assisted extraction of total flavonoids from *Abrus cantoniensis* (Abriherba) by response

surface methodology and evaluation of its anti-inflammatory effect. Molecules 27:2036

Zamora R, Vodovotz Y, Billiar TR (2000) Inducible nitric oxide synthase and inflammatory diseases. Mol Med 6:347–373

Zhang H et al (2020) Therapeutic potential of TNFα inhibitors in chronic inflammatory disorders: past and future. Genes Dis 8:38–47