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THE IMPACT OF HUANG QI GRANULES ON THE INTERLEUKINS, TUMOR NECROSIS FACTOR A AND CELLULAR IMMUNE FUNCTION IN PATIENTS DIAGNOSED WITH ACUTE KAWASAKI DISEASE

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Abstract

Background and Objective: *Cytokines are proteins that play an essential role in the process of inflammatory tissue damage and govern immunological responses, both of which have the potential to affect the progression of Kawasaki disease. The purpose of this analysis was to explore the effect that Huang Qi granules had on the expression of inflammatory cytokines in peripheral blood mononuclear cells, specifically interleukin-1 β, interleukin-6, tumor necrosis factor α, and interleukin-8.*

Material and Methods: *In patients with Kawasaki disease, the peripheral blood mononuclear cells were analyzed for their levels of production of tumor necrosis factorα, interleukin-1β, interleukin-6, and interleukin-8. Both an ELISA test RT-PCR were utilized in order to determine the production levels. The measurements were taken before and after the oral consumption of Huang Qi granules at doses of 20 and 50 g.*

Results: *The treatment with Huang Qi granules significantly reduces the generation of interleukin-1β, interleukin-6, tumor necrosis factor α, and interleukin-8 in peripheral blood mononuclear cells in a dose-dependent manner. Huang Qi granules reduced four cytokine mRNA expressions. The inhibitory effects of Huang Qi granules may vary with cytokines.*

Conclusion: *The intricate cytokine profile resulted in peripheral blood mononuclear cells after Huang Qi granule therapy showed a role in decreasing inflammation and modulating immune cell functions. Huang Qi granules reduced cytokine expression, suggesting this discovery could be important. If further research along these lines is conducted, it could help progress the development of novel treatment strategies for Kawasaki disease*

Keywords: *Kawasaki disease, cytokines, Huang Qi granules, interleukin, tumor necrosis factor*

Introduction

Acute systemic vasculitis symptom Kawasaki disease (KD) affects children under four [*Kawasaki T., 1967*]. The main problems associated with this condition encompass the development of intracoronary artery thrombosis and coronary artery aneurysms. Recent clinical investigations have indicated that macrophages and monocytes become activated during the acute phase of KD. Despite the fact that the etiology of KD is still unknown, this has been shown to be the case

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[*Burns J et al., 1996*]. Furthermore, the dysregulation of cytokine production may have a role in developing the disease [Shulman S., 1989]. Recent research has documented the activation of immune cells in individuals with KD, with innate and adaptive immune systems playing a role in this phenomenon [*Lin C et al., 1992*; *Rowley A et al., 2011*; *McCrindle B et al., 2017*]. One potential mechanism that could contribute to the initiation of Kawasaki disease is the inflammatory damage inflicted upon vascular endothelial cells [*Jia C et al., 2019*]. Endothelial cells are of critical significance in maintaining blood vessel integrity, hence having control over inflammation and vascular function via intricate mechanisms [*Wu K., 1992*]. These mechanisms encompass the transportation of oxygen and energy and the regulation of tumor immunity and cellular metabolism [*Uldry E et al., 2017*].

The Huang Qi (*Astragalus membranaceus*) comprise traditional Chinese medicinal plants, including astragalosides [*Cao J et al., 2014*]. Pharmacological research has demonstrated that astragalosides exhibits anti-inflammatory properties, modulates the immune system, possesses anti-allergic effects, enhances microcirculation, and promotes tissue regeneration [*Lans, C., 2019*]. Previous study has confirmed the potential of astragalosides to effectively stimulate the production of type 1 T helper cytokines, including interferon-alpha and interferon gamma, in both human and mice. The combination of astragalosides with interferon-alpha demonstrates a synergistic effect, resulting in the enhancement of natural killer cell activity. Consequently, natural killer cells release cytokines, including interferon gamma and interleukin-2. Moreover, it possesses the capability to activate macrophages, resulting in the production of various cytokines, including interferon-alpha and interleukin-1. The cellular immune response is increased through the synergistic effect of these cytokines. Therefore, these granules have distinctive characteristics compared to other polysaccharide medications, positioning them as an ideal immune modulator [*Yakubogullari N et al., 2023*].

Traditional Chinese medicine exhibits favorable tolerance and can decrease the possibility of disease recurrence through prolonged maintenance treatment. The efficacy of many Chinese medicines in treating KD patients has been confirmed by validating their inflammatory cytokines and cellular immunological activities [*Choi J et al., 2022*]. Cytokines are recognized for their substantial involvement in mediating the link between inflammatory and immunological responses in many disease states, as they exhibit biological impacts on the host's inflammation and immune system responses [*Fung P., Kong R., 2016*]. However, there is a lack of comprehensive understanding regarding the influence of Huang Qi granules on the composition of essential cytokines, specifically interleukin-8 (IL-8), interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), and interleukin-6 (IL-6), which are produced by immune cells.

There is currently no documentation of the use of Huang Qi granules in the treatment of KD, and there is no evidence to support treating KD directly with Huang Qi granules. The main aim of this study was to examine the therapeutic performance of Huang Qi granules in the management of KD while also revealing the underlying mechanism of action. It was based on the situation described above, and it included consideration of the characteristics of astragalosides as well as the pathophysiology of KD. Therefore, the main objective of this study was to assess the *in vitro* effects of Huang Qi granules on the release of TNFα, IL-8, IL-6, and IL-1β by peripheral blood mononuclear cells (PBMCs) collected before and following treatment with KD.

Materials and Methods

Preparation of PBMCs and culture procedures: Patients who had been diagnosed with KD, as per the diagnostic criteria outlined in the recommendations set forth by the American Heart Association, participated between March 2023 and July 2023. All children included in this study had an onset time within 7 days and did not receive any intravenous immunoglobulin treatment before admission, nor were they administered nonsteroidal anti-inflammatory medicines, steroids, or immunosuppressive medications within 2 weeks following admission. In the study, children with incomplete KD and other notable medical problems were excluded from the study population. There

were no cases of coronary artery lesions or significant consequences observed among the subjects in this trial.

Twenty-one children who were in good health and aged between 2 and 4 years were assigned randomly to participate in the Huang Qi group (n=14) or the control group (n=7). The study consisted of prescribing oral Huang Qi granules in two groups of patients, with dosages of 20 *g* (n=7) and 50 *g* (n=7), three times each day for 12 weeks [*Li L et al., 2013*]. PBMCs were collected from human volunteers using the dextran sedimentation method following Ficoll density-gradient spinning (Amersham Pharmacia Biotech), previously described [*Chang L et al., 2006*]. The buffy coats were collected through two rounds of washing. The purified PBMCs were cultivated in RPMI-1640 medium (Gibco), which was added with 100 *U/mL* of penicillin G sodium, 0.25 *μg/mL* of amphotericin B, 100 *μg/mL* of streptomycin sulfate, and 10% heat-inactivated fetal bovine serum (Gibco) [*Hung S et al., 2000*].

Before cytokine analysis, culture supernatants were collected, aliquoted, and kept at -85°C using the enzyme-linked immunosorbent assay (ELISA) method. The cell concentration used in cytokine mRNA expression studies varied from $3\text{-}4\times10^6$ *cells/mL*. The tests and measurements were performed in three experiments. Each round of incubation ended with cellular viability testing, and the supernatants were collected, maintained at -85°C, and analyzed by ELISA. After that, the cell pellets were treated to purify RNA and analyze it using reverse transcription polymerase chain reaction (RT-PCR).

ELISA analysis: The concentrations of IL-8, IL-6, TNFα, and IL-1β in the culture supernatants were measured utilizing solid-phase sandwich ELISA kits. The experiments were conducted in triplicate, utilizing the following particular kits: EH3TNFA, and EH2IL8, EH2IL6 (Pierce Biotechnology, USA), and the Hu IL-1β kit (BioSource International, USA). The manufacturer's recommendation was followed during the assay process. The ELISA kits exhibited sensitivities (lower detection limits) of 2, 1, 2, and 1 *pg/mL* for TNFα, IL-6, IL-8, and IL-1β, respectively. To summarize, a volume of 50 *μL* of the sample was used for each well in triplicate. Subsequently, the sample was incubated with a biotinylated antibody targeting TNFα, IL-6, IL-8, or IL-1β. This was followed by another incubation step involving the substrate 3,3',5,5'-tetramethylbenzidine and streptavidin-horseradish peroxidase. The plates performed a washing process consisting of three to four repetitions prior to each incubation phase. The absorbance measurement at a wavelength of 450 *nm* was performed using an ELISA reader (EL 312e Microplate, BIO-TEK Instruments, USA). The determination of cytokine concentrations in every single well was conducted using the standard curve generated from pure cytokines. The measurement of cytokine concentrations in each sample was achieved by computing the mean value of replicated experiments.

RT-PCR analysis: After collecting the treated cell pellets, a one-step extraction of total RNA from each sample was performed using the Trireagent-RNA isolation reagent (Molecular Research Centre, USA). The RT-PCR method was used in this work to investigate gene expression. The RT was carried out in the following manner: At 70°C for 10 min, a DEPC water solution (16 *μL*) contained 11 *pmoles* of oligo $(dT)_{18}$ primer (Protech Technology Enterprise, Taiwan), and 2 *μg* of total RNA. After that, it was left to chill for 5 min on ice. Following that, the primer was added with 2 *μL* of 11 *mM* dNTP, 3 *μL* of 11 StrataScript buffer (Stratagene, USA), and 2 *μL* of 50 U StrataScript reverse transcriptase in a single vial. The solution mixture was then centrifuged at 4°C for 11 *min*. After incubation at 43°C for 52 min and at 75°C for 17 *min*, cDNA products were collected and kept at -20°*C* until analysis. The amount of cDNA necessary for PCR amplification was 80 *ng* of total RNA. In the 20 *μL* amplification mix, there was Taq DNA polymerase (1 unit), 4 *mM* dNTP, 1 reaction buffer (MoBiTec GmbH, Germany), and 10 *pmoles* of a particular primer (Clontech Laboratories, USA). Table 1 illustrates the primer pairs utilized in this investigation and their associated annealing temperatures.

Negative controls were conducted in the study by employing either an RNA sample derived from cells that received treatment or a buffer-only solution. The reaction mixture was exposed to a heating process at a temperature of 95°C for 5 minutes. Subsequently, the mixture followed

Table 1.

The annealing temperatures and primer sequences utilized in this research

Primer name		Sequences (5'-3')	Annealing temperature	Product size (bp)	Reference
TNFα	F	GAGTGACAAGCCTGTAGCCCATGTTGTAGCA	57°C	444	[*Pennica D et al., 1984*]
	R	GCAATGATCCCAAAGTAGACCTGCCCAGACT			
IL-6	F	ATGAACTCCTTCTCCACAAGCGC	55°C	628	[*Hirano T et al., 1986*]
	R	GAAGAGCCCTCAGGCTGGACTG			
IL-8	F	ATGACTTCCAAGCTGGCCGTGGCT	60°C	289	[*Mukaida N et al., 1989*]
	R	TCTCAGCCCTCTTCAAAAACTTCTC			
IL-1β	F	ATGGCAGAAGTACCTAAGCTCGC	62°C	802	[*Auron P et al., 1984*]
	R	ACACAAATTGCATGGTGAAGTCAGTT			
GAPDH	F	TCAAGATCATCAGCAATGCCTCC	55	190	[*Efati Z et al., 2023*]
	R	GCCATCACGCCACAGTTTC			

Notes: *GAPDH- Glyceraldehyde-3-phosphate dehydrogenase*

amplification through a set of 24-31 cycles, each consisting of a 2 min incubation at 96°C, followed by a 2 min annealing step at the specified temperature, and finally, a 2 min elongation at 73°C. The experiment concluded with a final extension step conducted at a temperature of 73°C for 11 min. The PCR results were applied onto a gel containing a 2% agarose to facilitate the procedure of electrophoresis. The gels were subjected to ethidium bromide staining, and further photographic documentation was performed.

Statistical analysis: The statistical application SPSS 10.0 (SPSS Inc. in Chicago, Illinois, United States) was utilized in order to carry out the Mann-Whitney test. For a difference to be considered statistically significant, the significance level is required to be below 0.05.

Results

Protein production of IL-8, IL-1β, TNFα, and, IL-6 in PBMCs after treatment with Huang Qi granules:

The possible effects of Huang Qi granules on the generation of IL-8, IL-1β, TNFα, and IL-6 in PBMCs were examined. 20 and 50 *g* Huang Qi granules significantly reduced the production of all 4 cytokines in cells (Fig. 1). However, the impact of Huang Qi granules on the secretion of IL-8 was shown to be restricted in comparison to other cytokines.

mRNA expression of IL-8, IL-1β, TNFα, and, IL-6 in PBMCs after treatment with Huang Qi granules

Compared with the control group, oral consumption with 20 and 50 *g* Huang Qi granules decreased the mRNA expression of IL-8, IL-1β, TNFα, and, IL-6 in PBMCs (Fig. 2). Huang Qi granules, on the other hand, had a minimal impact on the amounts of IL-8 transcripts. According to

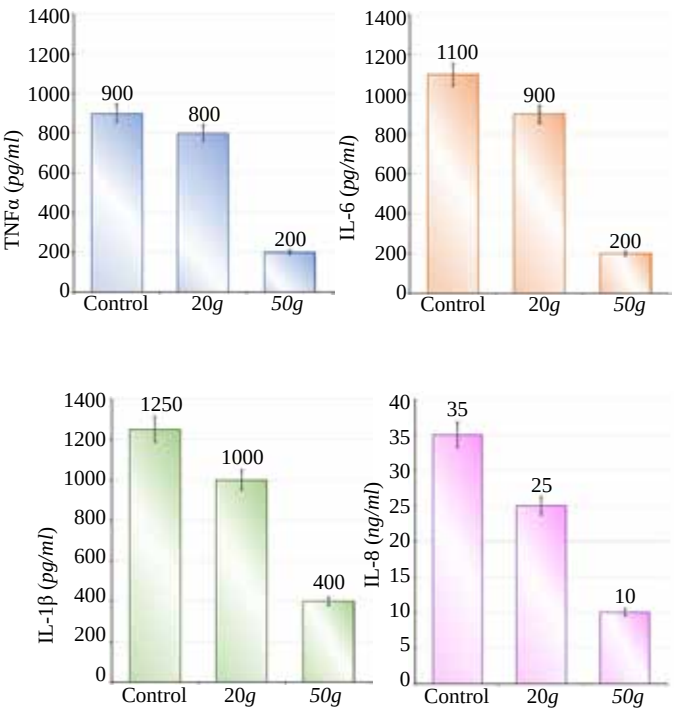

Figure 1. *Effects of Huang Qi granules on cytokine production in treated PBMCs. In the experimental group, participants orally received granules containing 20 and 50 g of Huang Qi granules. The amount of (A) TNFα, (B) IL-1β, (C) IL-6, and (D) IL-8 in the culture supernatants were measured using ELISA. The data are presented in the format of the mean ± standard error, which has been calculated based on a minimum of three independent experiments. Statistically significant differences between the treated and control groups are indicated by specific symbols: **< 0.01; *< 0.05.*

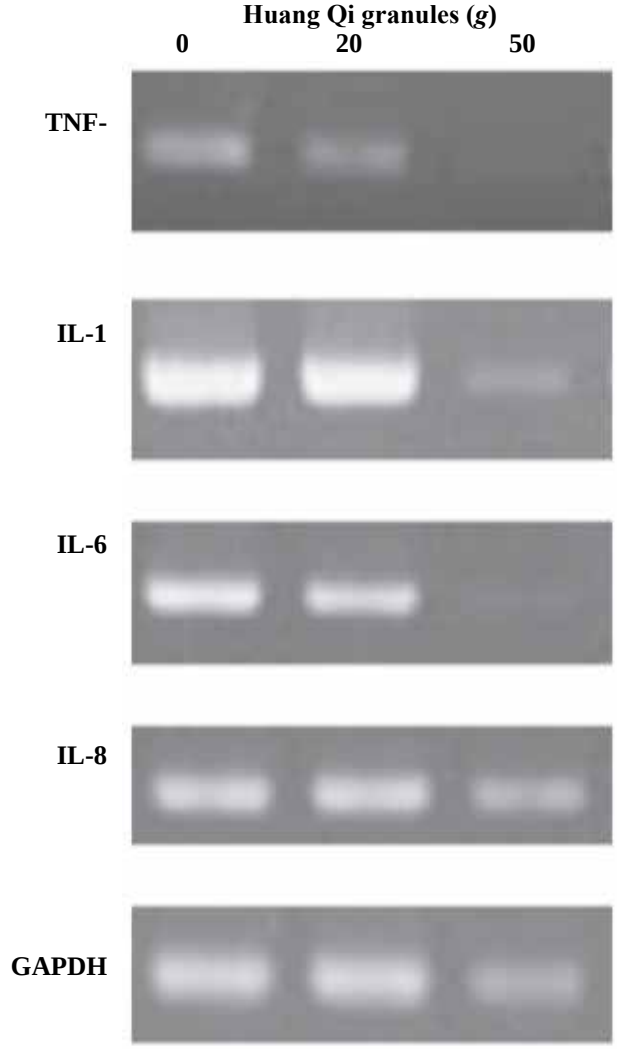

Figure 2. *Effects of Huang Qi granules on mRNA expression of cytokines in treated PBMCs as measured using the RT-PCR assay. In the experimental group, participants orally received granules containing 20 and 50 g of Huang Qi granules. The following illustrations show representative findings from three separate tests using amplified sequences specific for IL-8, IL-6, TNFα, and IL-1 β, respectively, as well as GAPDH.*

the findings, Huang Qi granules might play a part in the process by which immune cells express their cytokine genes. The findings also suggested that the inhibitory impacts of Huang Qi granules on various cytokines can be distinct from one another.

Discussion

The progression of inflammatory diseases such as KD is caused by the sustained and/or increased release of cytokines (IL-8, IL-1β, TNFα, and, IL-6) in inflamed tissues [*Furukawa S et al., 2008*]. Due to its participation in the activation of human coronary artery endothelial cells in response to S100A12 chemoattractant to monocytes [*Armaroli G et al., 2019*], the involvement of IL-1β in the aetiology of KD has been demonstrated. This pro-inflammatory cytokine exhibits increased levels during the acute phase of KD [*Cavalli G et al., 2021*]. IL-1β is synthesized by immune cells that have been activated, as well as by endothelial cells. It facilitates the synthesis of more cytokines, including IL-8 and IL-6, and triggers the upregulation of adhesion molecules on endothelial cells [*Pang G et al., 1994*]. IL-1β additionally contributes to the induction of fever, systemic inflammation, and the stimulation of endothelial cells, which are crucial in the pathogenesis of coronary artery anomalies [*Abbate A et al., 2020*].

TNFα exhibits notable similarities in its biological properties to IL-1β and demonstrates synergistic effects when combined with IL-1β [*Dinarello C., 1991*]. In KD, increased levels of TNFα have been observed during the acute phase of the illness [*Furukawa S et al., 1994*]. TNFα contributes to the recruitment and activation of immune cells (T cells and macrophages), at the site of inflammation. It also promotes the production of adhesion molecules, which facilitate the migration of immune cells into the vessel wall [*Chi Z., Melendez A., 2007*]. IL-6 is a pleiotropic cytokine that the serum level of this cytokine is significantly elevated in patients with KD, suggesting its involvement in the pathogenesis of the disease [*Su Y et al., 2019*]. IL-6 is of significant importance in controlling the immune cellular response and the regulation of the acute-phase reaction. It promotes the growth and activation of immune cells (T cells and B cells). IL-6 induces the production of acute-phase reactants, such as C-reactive protein [*Hirano T et al., 2021*]. The overproduction of IL-6 is implicated in the pathogenesis of systemic inflammation and the formation of coronary artery abnormalities [*Yudkin J et al., 2000*]. IL-8, a chemokine, exhibits significant chemotactic properties that promote the accumulation of granulocytes at inflammatory sites. Elevated levels of IL-8 have been observed in KD [*Asano T., Ogawa S., 2000*]. IL-8 is produced by various cell types, including endothelial and immune cells, in response to inflammatory stimuli. It facilitates the recruitment of neutrophils to the site of inflammation and leads to an increase in the inflammatory response [*Russo R*

et al., 2014]. IL-8 plays an essential part in the initiation and progression of vascular inflammation, as well as the formation of coronary artery anomalies in KD [*Su Y et al., 2019*].

Previous studies have not demonstrated a decline in the expression of TNFα, IL-8, IL-1β, and, IL-6 in PBMCs after consumption of Huang Qi granules. The current investigation exhibited a dose-dependent reduction in the secretion of TNFα, IL-8, IL-1β, and, IL-6 in PBMCs stimulated with Huang Qi granules. The rate at which transcripts of these cytokines were synthesized was similarly seen to decrease following treatment with Huang Qi granules. To the best of our current understanding, this study is the initial investigation that has provided a clear definition of the cytokine expression in cells treated with Huang Qi granules. The results indicate a significant involvement of Huang Qi granules in the reduction of inflammatory reactions and perhaps in the regulation of immune cell functioning.

Studies have shown that Huang Qi granules can inhibit inflammation and reduce the levels of pro-inflammatory cytokines in various disease models. In a study on juvenile collagen-induced arthritis rats, Huang Qi granules were found to ameliorate symptoms, reduce pro-inflammatory cytokine levels, and inhibit the expression of pyroptotic proteins involved in programmed cell death [*He T et al., 2019*]. Another study on adriamycin nephrosis in rats demonstrated that Huang Qi granules significantly reduced renal injury, proteinuria, and inflammation, possibly through the inhibition of inflammatory cytokine expression and macrophage infiltration [*Zhu C et al., 2011*]. Additionally, Huang Qi granules have been shown to improve nonalcoholic fatty liver disease by suppressing the NF-κB inflammatory pathway [*Lian B et al., 2022*]. Furthermore, in an ovalbumin-induced asthma model, Huang Qi granules were found to regulate the Th1/Th2 and Treg/Th17 balance, indicating their potential in inhibiting the development and severity of asthma [*Huang Z et al., 1993*].

Therefore, the identification of a particular ingredient or constituents that may have caused the reduction in secretion of TNFα, IL-8, IL-6, and IL-1β is challenging. However, additional research is required in order to understand the specific mechanisms by which these interventions operate comprehensively and to explore every aspect of their influence on the regulation of cytokines.

Conclusion

In the present study, the secretion of TNFα, IL-1β, IL-8, and, IL-6, and the mRNA expression of these cytokines in Huang Qi granules-stimulated PBMCs were examined. The consumption of Huang Qi granules resulted in a reduction in the production of several inflammatory cytokines in PBMCs. The results imply that oral consumption of Huang Qi granules might decrease inflammatory reactions and regulate the immune system functions. Targeting these cytokines and their signaling pathways with therapies, such as Huang Qi granules and other immunomodulatory agents, is an essential approach in the treatment of KD. However, the medical relevance of these discoveries has yet to be determined. Conversely, this work holds potential significance as it may contribute to the advancement of innovative therapy approaches for KD.

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