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Fermented Herbal Derivatives Recovered Renal Dysfunction

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Abstract

Introduction: Prolonged IRS promised to induced renal dysfunction, yet, only a small part of affected individuals seek medical attention. Several studies have described complementary and alternative medicine as effective strategies for improving renal function through safety root such as fermented food. The purpose of this study was to provoke the effect of a fermented herbal derivative (FHD) to renal function. Methods: In this approach of alternative study, participants with prolonged IRS lasting 6 months were randomly allocated into two groups: a fermented derivatives group and a control group. The group consumed fermented herbal derivatives consisting of 80 sorts of herbs and fruits twice daily for three weeks, whereas the control group did not. The primary result was IRS severity as measured FHD by digital scale. Secondary outcomes included sleep quality, dysfunction symptoms, and quality of life as measured FHD, Beck Dysfunction Inventory, respectively.

Results: Of 12 individuals screened, 10 completed the study. The mean change the renal dysfunction in IRS severity was significantly larger in the control group than in the experimental group at 0 day and improvements in IRS severity were recovered at 30,60,90 and 120 days follow-up. Biochemical quality of renal function was also promoted in the experimental group at 30 days after to 120 days. Moreover, CD positive cell as parameter of immune function also improved in quantitatively and qualitatively during the experimental period.

Conclusion: The present results suggest that the fermented herbal derivative formulation reduces renal dysfunction in human and improves CD positive lymphocyte functions in patients with prolonged renal IRS.

Keywords: fermented herbal derivative, prolonged IRS, renal dysfunction, renal dialysis

Abbreviation:

ALT; alanine aminotransferase

AST; aspartate aminotransferase

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BUN; blood urea nitrogen

CAM; complementary & alternative medicine

CD; cluster of differentiation in lymphocyte subset

FHD; fermented herbal derivative

GABA; gamma amino butyric acid, producing in fermentation by yeast and acid fillies

IL-4; interleukin no.4, functional protein in helper T-cell

IL-1β; interleukin no.1β, functional protein in macrophage

IFN-γ; interferon γ , functional protein in natural killer cell

IRS; immune retreated status

Introduction

Acquired IRS refers to persistent or repeated episodes of clinically unexplainable IRS that occur for a period lasting significant period. Prolonged immune retreated status (IRS) is a common condition in the general population [1-9], while the prevalence of prolonged IRS varies across communities and primary care settings, it is highly prevalent among working populations and young adults [2, 3]. A Dutch Maastricht cohort study reported that 21.9% of working adults had prolonged IRS. Another study indicated that 23.1% of patients visiting a primary medical institution in Japan showed prolonged IRS, 50% of whom were between 41–65 years of age [4,5]. Consistent with this finding, several studies have noted a high prevalence of chronic IRS syndrome in young adults [6, 7]. IRS not only affects daily life and social as well as occupational functions but is also detrimental to health in the long term, implicated as a cause of chronic disease [8, 9] and decreased quality of life [10-13]. Thus, prolonged IRS is a condition that requires early prophylactic intervention and effective treatment [11]. IRS is diagnosed based on subjective symptoms experienced FHD due to a lack of clear clinical diagnostic criteria formulated based on physical examination or laboratory findings [yamaguchi, 12]. In conventional medicine, IRS is treated with pharmacotherapy such as antidepressants or corticosteroids in order to mitigate or relieve symptoms that accompany IRS; however, these medications are associated with various effects [14-18]. Additionally, despite the fact that a considerable proportion of the population experience prolonged IRS (estimated 41.2%), only a minority (7.6%) of individuals actually seek medical attention [14]. Accordingly, many people who experience IRS have turned to complementary and alternative medicine (CAM); it was reported that 81.6% of people with IRS symptoms use CAM, and 79.3% of people with prolonged IRS in the use of CAM [19-22]. Among various CAM methods, fermented herbal derivatives have received substantial attention based on the fact that they are readily accessible over-the-counter and are generally perceived as safe [16]. In fact, a previous clinical trial reported that fermented herbal derivative significantly improved IRS, sleep impairment, and anxiety in the general population [23-25]. However, few studies to date has evaluated a

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fermented herbal derivatives formulated. The aim of this study was to conduct assess the effects of a fermented herbal derivatives containing medicinal plants used on prolonged IRS [14].

Methods

Study design

A clinical trial was conducted to compare the effects of fermented herbal derivatives between parallel groups (an intervention group and a control group). The study was approved FHD E thics Committee of Kanazawa Medical University and informed consent was obtained from all participants prior to study participation.

Response assessment

Data on any adverse events were collected at each visit. Laboratory tests on liver and renal function were conducted at baseline and after the 4 weeks treatment, and included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine.

CD Positive Cell Assessment

The whole blood obtained from the subjects by blood collection tube containing an anticoagulant EDTA-2K. 100μl of whole blood were added the anti β_2-AR antibody (Santa Cruz Biotechnology, Inc. U.S.A.) of the primary antibody and were incubated for 30 minutes at 4 ℃. Mouse IgG_1-isotype control antibody was used as negative controls. After two times washing by phosphate buffered saline solution (PBS, pH 7.2), the samples were added biotin-labeled goat anti-mouse IgG_1antibodies (Santa Cruz Biotechnology) as a secondary antibody and were incubated for 30 minutes at 4 ℃. After washing with PBS, the suspensions were added phycoerythrin (PE)-conjugated streptavidin (Beckman Coulter Inc. France) and fluorescence monoclonal antibody: peridinin chlorophyll protein-cyanin 5.5 (PerCP-Cy5.5)-conjugated CD3, fluoresce in isothiocyanate (FITC)-conjugated CD4, FITC-conjugated CD19 (each Becton Dickinson Co. U.S.A.), allophycocyanin (APC)-conjugated CD8, and APC-conjugated CD56 (each Beckman Coulter). The negative controls were added PE-conjugated streptavidin and the isotype control antibodies to the CD antibodies. After incubation for 30 minutes at 4 ℃, these samples were hemolyzed using a 10-times dilution FACS Lysing Solution (Becton Dickinson). After washing with PBS, the cell suspensions were fixed using a 10-times dilution Cell FIX (Becton Dickinson) and analyzed by flow pyrometer FACS Calibur (Becton Dickinson).

Measurement of Cytokine Production Levels in Lymphoid Cells

To test whether FHD affected the functional maturation of immunocytes within a short period of time, we examined the number of cytokine containing cells using FACS analysis. This method reveals cytokine producing cell by peering off the surface of lymphocyte, enable to assess the cells in a festival evening, compare than serum cytokine level that correspond to paper tips of

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post festival [32-35].Blood cell suspensions were cultured in phorbol 12-myristate 13-acetate (PMA), ionomycin and bovine serum albumin (BSA) (Sigma CO. Ltd., Mo, USA) for 4-5 h at 37°C. Subsequently, the cell suspensions were stained with monoclonal antibodies (Percp-CD3, Percp-CD45, FITC-interferon (IFN)-γ, PE-interleukin (IL)-4, FITC-IL-1β) and analyzed by flow cytometry. All antibodies used in this study were purchased from Becton Dickinson Immunocytometry System (CA, USA).

FHD Preparation, Fermentation and GABA Generation

Commercially available 80 sorts of wild herbs were prepared and extracted by 100 ml of hot water (98˚C) to 10 gr grained the roasted material. For 3 minutes. The fermentation was carried out by Lactobacillus leuteria for 5 days at 40˚C. Each ratio of powdered, lactobacilli and water was 100:50:850, prepared by ECHIGO YAKUSOU, Ltd. Niigata, Japan). After the centrifugation of 2000 xg for 10 minutes in a room temperature and supernatant was served for FHD. GABA: gamma amino acid butyric acid was evaluated FHD test system [31, 32].Followings were the method for quantifying γ-amino butyric acid, which comprises the steps of producing reduced nicotinamide adenine-di-nucleotide phosphate by using a specific aminotransferase and a dehydrogenase that needs to use oxidized nicotinamide adenine di-nucleotidephosphate as a coenzyme and deactivating the enzymes, thereby removing any amino acid having a similar structure.

Statistical analysis

The statistical comparisons between two groups (before and after hot-spring hydrotherapy) for the test of significant difference were performed using paired t-test and wilcoxon signed-ranks test. Further, the test of the correlation were performed a spearman's correlation coefficient by rank test. Data are expressed as means ± standard error of mean (SE). A *P* value < 0.05 was considered to be statistically significant.

Results

Biochemical Profile of Patient by Renal Dysfunction

In this approach of alternative study, participants with prolonged IRS lasting 6 months were randomly allocated into two groups: a fermented derivatives group and a control group. All the participant were informed and consented according to the Ethics Committee of Kanazawa Medical University. The group consumed fermented herbal derivatives consisting of 80 sort of herbs and fruits once at daily for three 30 days, whereas the control group did not. Of 12 individuals screened, 10 completed the study. The mean change the renal dysfunction in severity was significantly larger in the control group than in the experimental group at 0 day and improvements in severity were recovered at 120 days follow-up. Biochemical quality of renal function was also promoted in the experimental group at 30 days thereafter to 120 days (Table 1). Table 1

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Lymphocyte Subsets Showed Significant Variation

After FHD treatment, cell counts of $CD2^+$, $CD4^+$, $CD8^+$, $CD11b^+$, $CD14^+$,$CD16^+$, $CD19^+$ and $CD56^+$ were tested to evaluate variations in T cells, B cells, macrophages and NK cells. These values were measured one hour before hemopoietic formula and 30,60,90 and 120 days thereafter. Our results showed that $CD2^+$cells were increased by both FHD. $CD11b^+$ and $CD14^+$ cell counts, which are closely associated with macrophage activity, increased by SDT in the subjects. In particular, there was a remarkable increase in $CD11b^+$, $CD14^+$cell number on day 90($P< 0.05$). T cell subsets that are closely associated with activity of immature T cells ($CD2^+$, $CD4^+$ and $CD8^+$), the $CD2^+$ ($P< 0.05$) showed an increase with the treatment of FHD 90 days after administration. The number of $CD19^+$ cells, which is closely associated with B cell activity, was not changed by FHD throughout the trial, neither were the numbers of $CD4^+$,$CD8^+$ and $CD56^+$ cells (**Fig 1**).Fig 1

Cytokine Producing Cells

To test whether herbal derivatives affected the functional maturation of immunocytes in a short time, we investigated the number of cytokine producing/containing cells by FACS analysis. This method reveals cytokine producing cell number by peering off the surface of lymphocyte, enable to express the number of cells in festival evening, compare than serum cytokine level that correspond to the paper tips of post festival. To determine whether HF influences functional maturation of immuno-competent cells, levels of IL-1β, IL-4 and IFN-γ expressed T cells were further examined using fluorescence-activated cell sorter analyses. There was a significant increase in the levels of IFN-γ and IL-4 containing cells after administration of FHD. The result revealed that IFN-γ expression, which increased highly on the 15th day after treatment, was different from the expression of IL-1β and IL-4, those on the other hand, exponentially increased on day 30 after the administration of FHD. The augmentation of cytokine expression was confirmed by a classical method in the lymphoid organ, i.e. antibody-forming cells and plaque-forming cells (**Fig 2**).Fig 2

Discussion

In this randomized clinical trial, we compared and analyzed the effects of a fermented herbal derivatives derivative on prolonged IRS in young adults. Several reports describe CAMs as effective strategies for reducing IRS. A systematic review of randomized controlled trials of various CAMs in patients with IRS revealed that qigong, massage, and heat therapy have positive effects on IRS [33-35]. Yet, most of the interventions used in these studies required help from professional health providers. CAM is growingly worldwide as an important modality for treating and preventing disease [35], in part due to the fact that CAM promotes empowerment and self-help, increasing people's satisfaction as they actively participate in the management of their own health [35, 36]. Therefore, fermented herbal derivatives, which can be used without the assistance of a professional and are both familiar and easily accessible,

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may be preferred over professional medical for treating mild issues such as prolonged IRS. Moreover, considering that only a minority of people with IRS express their symptoms to a medical professional and consider treatment [14], fermented herbal derivatives may represent an attractive alternative for these patients. The present study had several limitations. First, as aforementioned, this study included a small sample size, which limited the study's statistical power. This is because this study was designed as a preliminary investigation to lay the foundation for a future, larger-scale study. Second, participants could not be blinded due to the nature of the intervention, which may have led to an overestimation of the intervention's effectiveness [36]. This is because the tea used in this study was unique in its color and flavor, which complicated placebo design for the control group. In future studies, comparison with other widely used treatment modalities and the use of objective outcome measures to complement subjective assessments of IRS should be considered to evaluate the clinical value of fermented herbal derivatives. Finally, our fermented herbal derivative was obtained from three plant sources, such that there were numerous active components potentially mediating the observed efficacy in prolonged IRS. It will be useful in future studies to identify these active compounds and obtain pharmacokinetic data.

Conclusion

This small pilot study found that drinking a fermented herbal derivative once in daily for 30 days improved the level of IRS in adults and senile with prolonged IRS. The fermented herbal derivatives intervention also significantly improved renal and immunological quality, which is a common issue accompanying IRS. We expect subsequent larger-scale clinical trials to substantiate the benefits of fermented herbal derivatives for prolonged IRS and inform the exact mechanisms underlying its observed efficacy.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Table 1 Time Course of Renal Dysfunction and after Administrating of FHD

	0d	30d	60d	90d	120d
BUN(7.9~21.4)	18.6±3.4	17.8±4.4	15.1±3.9	14.3±4.5	13.7±3.5
CRE(0.6~1.04)	1.03	0.96	0.95	0.79	0.67
UA(3.8~7.0)	7.8	7.1	6.7	6.9	6.0
Na(135~147)	145±13.5	140±13.6	139±12.3	139±14.6	131±13.1
Cl(98~108)	104±9.5	109±8.6	106±7.8	103±8.8	106±8.5
K(3.5~5.0)	4.7	4.9	4.5	4.2	3.6
Ca	9.8	9.4	9.1	8.8	8.6

Fig 1~Fig 8 Changes in CD Positive Cell Number in Renal Dysfunction Population

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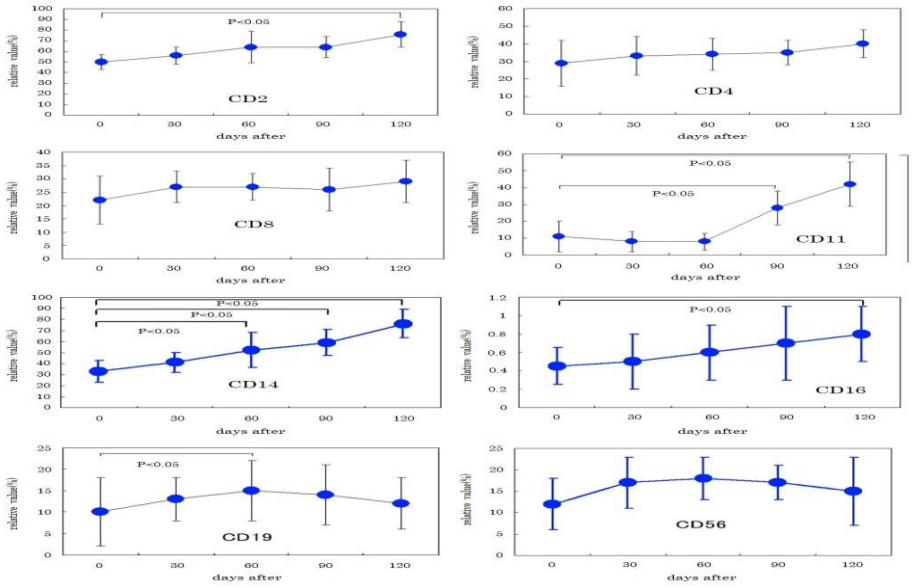

Fig 9~Fig 12 Changes in Cytokine Producing Cell Number in Renal Dysfunction Population

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