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Korean Red Ginseng Slows Depletion of CD4 T Cells in Human Immunodeficiency Virus Type 1-Infected Patients

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We have previously showed that long-term intake of Korean red ginseng (KRG) delayed disease progression in human immunodeficiency virus type 1 (HIV-1)-infected patients. In the present study, to investigate whether this slow progression was affected by KRG intake alone or in combination with HLA factor, we analyzed clinical data in 68 HIV-1-infected patients who lived for more than 5 years without antiretroviral therapy. The average KRG intake over 111.9 ± 31.3 months was 4,082 ± 3,928 g, and annual decrease in CD4 T cells was 35.0 ± 28.7/μl. Data analysis showed that there are significant inverse correlations between the HLA prognostic score (0.29 ± 1.19) and annual decrease in CD4 T cells ($r = -0.347$; $P < 0.01$) as well as between the amount of KRG intake and annual decrease in CD4 T cells ($r = -0.379$; $P < 0.01$). In addition, KRG intake significantly slowed the decrease in CD4 T cells even when influence of HLA class I was statistically eliminated (repeated-measure analysis of variance; $P < 0.05$). We also observed significant correlation between KRG intake and a decrease in serum-soluble CD8 antigen level ($r = 0.62$; $P < 0.001$). In conclusion, these data show that KRG intake independently and significantly affected the slow depletion of CD4 T cells irrespective of HLA class I.

The introduction of highly active antiretroviral drug therapy (HAART) has proven effective in the treatment of human immunodeficiency virus type 1 (HIV-1)-infected patients (15, 32). HAART alone, however, cannot eradicate the virus in the human body (9, 10, 33). On the other hand, production of Th1 cytokines is gradually reduced in HIV-1-infected patients (7, 8). Thus, the key immune modulator in cell-mediated immunity, interleukin-2 (IL-2), has recently been tried in combination with HAART. Although IL-2 therapy significantly increases the number of circulating CD4 T cells, it also has many limitations because of severe adverse effects. Thus, a new modality with safety is required for more effective therapy of AIDS.

In the Orient, *Panax ginseng* C. A. Meyer in particular has been used as a drug for more than 2,000 years (23). At present, ginseng is one of 12 medicinal herbs commonly used in America (28), as well as the most well-known and valued herb in Korea, China, and Japan. In particular, Korean ginseng is most expensively traded at the international market. Since the late 1960s, many studies have been performed to identify the active ingredients of ginseng and their functions. Ginseng is considered an adaptogenic agent which enhances physical performance, promotes vitality, and increases resistance to stress and aging and possesses immunomodulatory activity (27, 28, 31). The adaptogenic properties of ginseng are believed to be due to its effects on the hypothalamic-pituitary-adrenal axis (11, 14, 25).

Regarding its immunomodulatory properties, a study in normal human volunteers revealed that ginseng significantly increases neutrophil, CD4 T cell, and NK cell functions (27). Ginseng was also found to increases the cellular immune functions of peripheral blood mononuclear cells (PBMC) from AIDS patients and normal individuals (28). Recently an acidic polysaccharide from ginseng was shown to induce Th1 cell and macrophage cytokines (19), and this immunostimulating effect was blocked in the presence of antibodies to IL-2 and gamma interferon (22). Red ginseng acidic polysaccharide from Korean red ginseng (KRG) showed its usefulness as an adjuvant in cancer therapy (29). In addition, treatment of chronic *Pseudomonas aeruginosa* pneumonia in rats with ginseng was found to reduce bacterial load and lung pathology, as well as to increase immunoglobulin G2a in serum, suggesting that the antimicrobial properties of ginseng are due to its induction of Th1-like responses. In addition, xylanase and panaxagin from ginseng have been reported to possess inhibitory effects against HIV-1 reverse transcriptase (21).

Beginning in late 1991, we had an opportunity to treat HIV-1-infected patients with KRG for 6 months and observed that KRG intake had various beneficial effects including increases in the CD4 and CD8 T cell counts (6). We also found that there are significant inverse correlations between the duration of KRG intake and the mutation rate in the *env* gene in vivo and between the duration of KRG intake and the progression rate in HIV-1-infected patients (2). Data analysis over a period of 60 months revealed that KRG intake more significantly delays the decrease in CD4 T cells than zidovudine monotherapy as well as slowing the development of resistance to antiretroviral drugs (3, 4). Many patients have maintained their CD4 T cell counts for more than 10 years without antiretroviral drug therapy. Although the prognosis of HIV-1-infected patients has been found to be strongly associated with their HLA

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alleles (17–19, 21, 25), HLA alleles have never been determined in Korean HIV-1-infected patients. Thus, it is needed to rule out the possibility that the effects of KRG intake in our studies might be affected by the HLA factor.

In the present study, to investigate whether this slow progression or maintenance of CD4 T cells over 10 years was affected by KRG intake alone or in combination with HLA factor, we determined HLA class I in 90 patients and analyzed it with clinical data.

MATERIALS AND METHODS

Study population. Ninety HIV-1-infected patients diagnosed from 1987 to 2001 have been randomly recruited nationwide. At enrollment, patients were asked to return for an interview and for a clinical examination and a blood sample every 6 months. At baseline, 79, 8, and 3 patients were at U.S. Centers for Disease Control and Prevention stages A, B, and C, respectively. Of these 90 patients, 68, 18, and 4 patients acquired the virus through sexual contact, contaminated clotting factor 9, and transfusion, respectively. Because the interval from "infection focus" to "recruitment into HIV cohort" except for that of hemophiliacs was uncertain, estimating the rate of progression of HIV-1 infection was accomplished by measuring the annual decrease in CD4 T cells. The HLA results were compared with those of a control group, which was comprised of 199 uninfected Korean people drawn from the population. Twenty-two patients were treated with antiretroviral drugs or were monitored for less than 60 months. Thus, changes in CD4 T cells and correlation among KRG intake, CD4 T cells, and HLA were finally analyzed in the 68 out of 90 patients. The median follow-up time in the 68 patients was 113.5 months (range, 60 to 164 months).

Treatment with KRG. Sixty-one out of the 68 patients were treated with KRG, and 7 patients were not treated with KRG. The amount of KRG we supplied to each patient was 4,082 ± 3,928 g (range; 0 to 19,320 g), which corresponds to 25.2 months' intake with a daily 5.4-g recommended dose. Informed written consent was obtained from all study participants or their guardians.

Laboratory procedures. DNA was isolated from PBMC (6), and HLA-A, -B, and -C typing was performed using the amplification-refractory mutation system–PCR method. Each tube contained a primer mix consisting of the allele- or group-specific primer pairs, as well as a positive-control primer matching the nonallelic sequences. There were 32 sets specific for HLA-A, 27 sets specific for HLA-B, and 23 sets specific for HLA-C. PCRs were performed in a volume of 13 μl modified from the class I amplification-refractory mutation system–-PCR reference manual of the 12th International Histocompatibility Workshop. The PCR products were electrophoresed on 1.5% agarose gels prestained with ethidium bromide. Variants in transporter associated with antigen-processing genes (TAP) were identified by SSCP.

Assigning prognostic scores to HLA alleles or allele combinations. An HLA scoring profile was developed by means of a detailed analysis using Cox proportional hazards models to compute the relative hazards of AIDS following HIV-1 seroconversion in men carrying a given marker compared with all men not carrying that marker (16–18, 20, 24). Using these data, individual alleles or allele combinations associated with either extreme of disease progression were assigned an integer value, with −1 indicating an association with rapid progression and +1 indicating an association with long-term nonprogression (24, 26). Among the protective alleles were B27, B51, B57, and A25 with TAP2.3, A26 with TAP2.3, A32 with TAP2.3, B18 with TAP2.3 (19, 25, 27), and B14, Cw8, and Cw14 (13). Among the alleles associated with rapid progression were B37, B49, A28 with TAP2.3, A29 with TAP2.1, B8 with TAP2.1, A23 without TAP2.3, A24 with TAP2.1 or TAP2.3, B60 with TAP2.1 or TAP2.3 (13, 18, 24), and B35 with Cw4 (26). All other alleles received a value of zero. For each individual, the HLA score profile was calculated as the algebraic sum of the values given to each allele.

CD4 and CD8 T cell counts and soluble CD8 antigen level. After staining PBMC with phycoerythrin and fluorescein isothiocyanate-conjugated antibodies against CD4 and CD8 antigens, respectively (Simultest reagent; Becton Dickinson, San Jose, CA), and CD4 and CD8 T cells were measured with a FACScan flow cytometer (Becton-Dickinson). Serum-soluble CD8 antigen (sCD8) was measured by an enzyme-linked immunosorbent assay method (T cell Diagnostics, MA).

Statistical analysis. Data were expressed as mean ± standard deviation. Statistical significance was estimated by correlation coefficient, Student's two-tailed *t* test, and repeated-measure analysis of variance (ANOVA) (SPSS package version 12.0).

RESULTS

HLA. Except HLA-Cw7, the frequencies of HLA class I alleles did not show any statistical difference between the 90 HIV-1-infected patients and 199 normal controls without HIV-1 infection (18.6 versus 30.0%; relative risk = 1.87) ($P < 0.05$) (Table 1). The distribution of HLA prognostic score in 68 patients was ≥+2, +1, 0, −1, and ≤−2 in 13, 15, 21, 16, and 3 patients, respectively. Its mean was 0.29 ± 1.19.

Correlation between CD4 T cells and HLA prognostic score. CD4 T cell counts decreased 301.6/μl over 111.9 ± 31.3 months, from 518.4 ± 210.7/μl to 216.8 ± 178.9/μl, corresponding to an annual decrease of 35.0 ± 28.7/μl. There was a significant inverse correlation between the HLA prognostic score and the annual decrease in CD4 T cells ($r = -0.347$; $P < 0.01$) (Fig. 1). The means ± standard deviations of annual decrease in CD4 T cells of patients with HLA prognostic scores of ≥+1, 0, −1, and ≤−2 were 25.3 ± 26.7, 35.6 ± 21.0, 43.8 ± 33.1, and 73.9 ± 32.3, respectively.

Correlation between CD4 T cells and KRG intake. There was an inverse correlation between the annual decrease in CD4 T cells and the amount of KRG intake (35.7 ± 28.8 g/month) (total 4,082 ± 3,928 g) ($r = -0.379$; $P < 0.01$) (Fig. 2). To investigate whether KRG intake affected independently the annual decrease in CD4 T cells, we divided 68 patients into two groups with HLA scores of <0 and ≥0, and within the two groups and between two groups we independently compared the rate of CD4 T cell depletion in two groups according to KRG amount (≤2,700 g and >2,700 g) (Fig. 3A). In the group with HLA prognostic score <0, CD4 T cells decreased significantly from 679 ± 194/μl to 137 ± 136/μl (20.1% compared to baseline) in the 11 patients with KRG intake ≤ 2,700 g and from 518 ± 212/μl to 250 ± 160/μl (48.3% compared to baseline) in the 8 patients with KRG intake > 2,700 g, respectively. In the group with a HLA prognostic score ≥ 0, CD4 T cells decreased from 519 ± 201/μl to 171 ± 134/μl (32.9% compared to baseline) in the 21 patients with KRG intake ≤ 2,700 g and from 456 ± 201/μl to 273 ± 212/μl (59.9% compared to baseline) in the 28 patients with KRG intake > 2,700 g, respectively (Fig. 3B). Thus, we found that KRG intake significantly slowed the decrease in CD4 T cells even when influence of HLA class I was eliminated (repeated measure ANOVA $P < 0.05$). In the same way, we divided the 68 patients into two groups according to the amount of KRG intake (two groups of patients with KRG ≤ 2,700 g and KRG > 2,700 g) and separately analyzed the correlations between HLA prognostic score alone and changes in CD4 T cells. The HLA prognostic score alone also significantly affected the change of CD4 T cells ($P < 0.05$). Thus, our data show that both KRG intake and HLA factor independently affected the slow depletion of CD4 T cells in the present study.

The effect of KRG intake on sCD8 level. Information on the level of serum sCD8 was available in 47 out of the 68 patients. Forty-four patients treated with KRG showed a significant decrease by 27.4% from 675.0 ± 238.4 U/ml to 530.0 ± 187.5 U/ml over 57.9 ± 26.5 months ($P < 0.01$). In our previous study, the level of serum sCD8 was 231 ± 95 U/ml in the normal individuals (5). To determine whether the amounts of KRG intake affected sCD8 levels differentially, we divided 47 patients into two groups with KRG intake ≤ 2,700 g and KRG

TABLE 1. Frequency of HLA-A, -B, and -C specificities in the Korean population (90 HIV-positive patients versus 199 normal controls without HIV-1 infection)

No. (%) of patients			No. (%) of patients			No. (%) of patients		
HLA-A	HIV$^+$	Normal control	HLA-B	HIV$^+$	Normal control	HLA-C	HIV$^+$	Normal control
1	4 (4.4)	5 (2.5)	7	12 (13.3)	14 (7.0)	1	26 (28.9)	70 (35.2)
2	44 (48.9)	94 (47.2)	8	0 (0.0)	2 (1.0)	2	1 (1.1)	4 (2.0)
3	4 (4.4)	9 (4.5)	13	5 (5.6)	15 (7.5)	4	15 (16.7)	28 (14.1)
11	18 (20.0)	44 (22.1)	14	5 (5.6)	9 (4.5)	5	6 (6.7)	4 (2.0)
24	40 (44.4)	69 (34.7)	27	3 (3.3)	12 (6.0)	6	3 (3.3)	13 (6.5)
26	14 (15.6)	22 (11.1)	35	6 (6.7)	20 (10.1)	7[a]	27 (30.0)	37 (18.6)
30	6 (6.7)	25 (12.6)	37	1 (1.1)	2 (1.0)	8	14 (15.6)	37 (18.6)
31	7 (7.8)	2 (1.0)	38	3 (3.3)	5 (2.5)	9	13 (14.4)	35 (17.6)
32	2 (2.2)	19 (9.5)	39	3 (3.3)	1 (0.5)	10	28 (31.1)	66 (33.2)
33	26 (28.9)	77 (38.7)	44	17 (18.9)	51 (25.6)	12	8 (8.9)	12 (6.0)
			46	8 (8.9)	22 (11.1)	14	18 (20.0)	48 (24.1)
			48	6 (6.7)	8 (4.0)	15	2 (2.2)	11 (5.5)
			51	14 (15.6)	30 (15.1)			
			52	7 (7.8)	10 (5.0)			
			54	9 (10.0)	30 (15.1)			
			55	5 (5.6)	9 (4.5)			
			56	2 (2.2)	0 (0.0)			
			57	0 (0.0)	1 (0.5)			
			58	8 (8.9)	29 (14.6)			
			59	2 (2.2)	6 (3.0)			
			60	7 (7.8)	16 (8.0)			
			61	15 (16.7)	46 (23.1)			
			62	20 (22.2)	42 (21.1)			
			67	3 (3.3)	4 (2.0)			
			71	2 (2.2)	0 (0.0)			
			75	3 (3.3)	3 (1.5)			

[a] Frequency of HLA-Cw7 was higher in HIV-infected patients than in the normal controls (RR = 1.87, $P < 0.05$).

intake > 2,700 g. We independently analyzed the changes in sCD8. The group of individuals with high KRG intake showed a more significant decrease by 32% from 691.8 ± 244.6 U/ml to 475.9 ± 184.0 U/ml (Fig. 4), whereas individuals with low KRG intake did not show such decreases in sCD8. Similarly, analysis of the effects of HLA on changes in sCD8 did not show any significant correlations between HLA score and decreases in sCD8 (data not shown). Therefore, these results suggest that there is a strong correlation between the decrease in serum sCD8 and KRG intake ($r = 0.620$; $P < 0.001$).

DISCUSSION

In the present study, we performed analysis of the effects of KRG intake on CD4 T cells, sCD8, and HLA prognostic score. We observed that there were strong correlations between

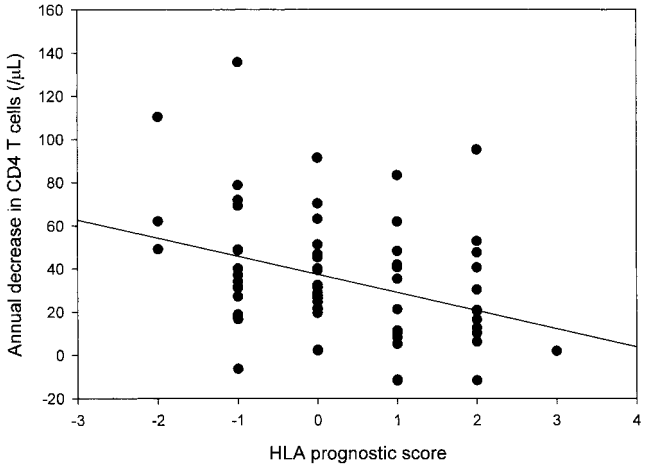

FIG. 1. Correlation between HLA prognostic score (0.29 ± 1.19) and annual decrease in CD4 T cells (35.0 ± 28.7/μl). There was a significant inverse correlation between HLA score and annual decrease in CD4 T cells ($r = -0.347$; $P < 0.01$).

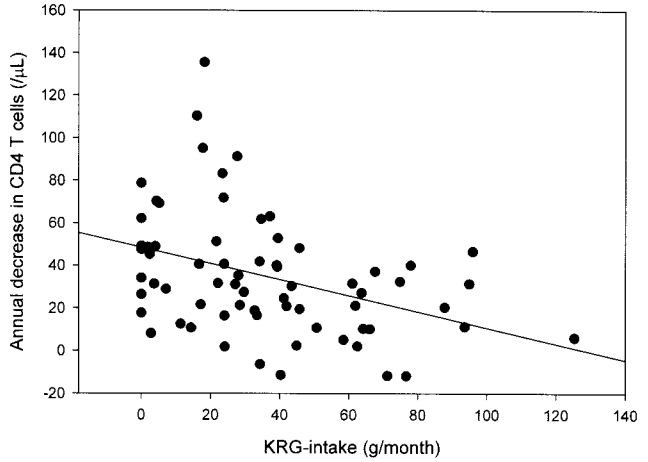

FIG. 2. Correlation between KRG intake (35.7 ± 28.8 g/month) and annual decrease in CD4 T cells (35.0 ± 28.7/μl). There was a significant inverse correlation between amount of KRG intake and annual decrease in CD4 T cells ($r = -0.379$; $P < 0.01$).

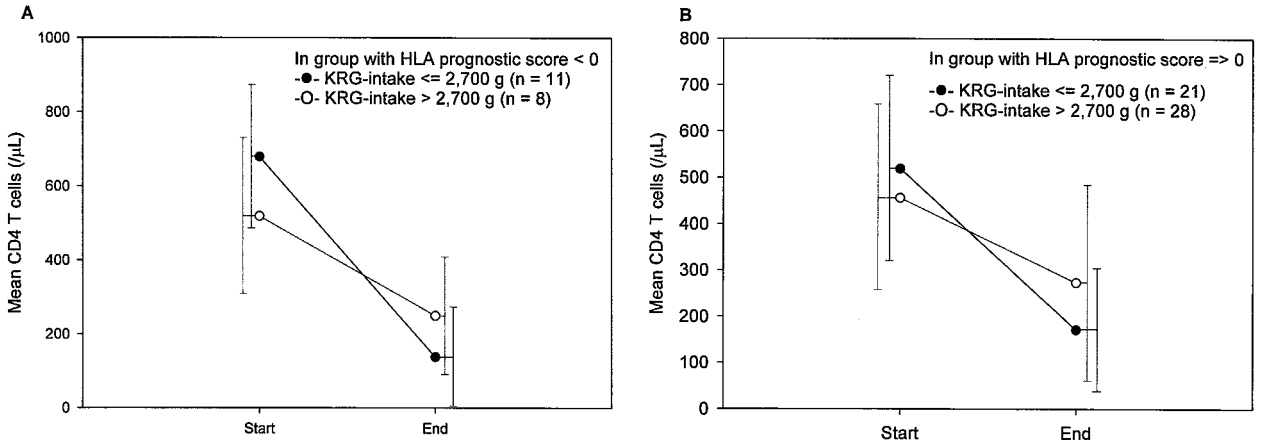

FIG. 3. Amount of KRG intake determines the rate of CD4 T cell depletion irrespective of HLA class I score. Sixty-eight patients were divided into two groups with HLA scores of <0 and ≥ 0 and in each group, patients were also divided into two groups according to amount of KRG intake ($\leq$2,700 g and $>$2,700 g). A. In the group ($n = 19$) with HLA prognostic score < 0, CD4 T cells decreased from 679 $\pm$ 194/μl to 137 $\pm$ 136/μl in the patients with KRG intake $\leq$ 2,700 g and from 518 $\pm$ 212/μl to 250 $\pm$ 160/μl in the patients with KRG intake $>$ 2,700 g, respectively. B. In the group ($n = 49$) with HLA prognostic score ≥ 0, CD4 T cells decreased from 519 $\pm$ 201/μl to 171 $\pm$ 134/μl in the patients with KRG intake $\leq$ 2,700 g and from 456 $\pm$ 201/μl to 273 $\pm$ 212/μl in the patients with KRG intake $>$ 2,700 g, respectively. KRG intake significantly slowed the decrease in CD4 T cells even when the influence of HLA class I was eliminated (repeated-measure ANOVA; $P < 0.05$). In the same way, HLA prognostic score alone also significantly affected the change of CD4 T cells ($P < 0.05$).

KRG intake and annual decrease in CD4 T cells and between KRG intake and sCD8, together with a significant inverse correlation between HLA prognostic score and annual decrease in CD4 T cells. In addition, we found that KRG intake alone slows the decrease in CD4 T cells irrespective of HLA prognostic score. This finding is actually evidenced by the fact that the annual decrease in CD4 T cells (35/μl) with a significant amount of KRG intake in this study was much lower than the natural decrease (70/μl) in the HIV-1-infected Korean patients without KRG intake (1).

Progression to AIDS is strongly associated with generalized activation of the immune system, manifested by elevated serum concentrations of neopterin, soluble IL-2 receptor, sCD8, and β_2-microglobulin, and with activation of a large proportion of CD8 T cells (12). From the long-term studies with KRG intake, one of the most consistent findings was a significant decrease in serum sCD8 (6), which is an immune activation marker physiologically secreted from CD8 T cells. Moreover, the significant and consistent decrease in serum sCD8 (19.2%) was maintained as long as KRG was taken continuously ($P < 0.01$) (Y. K. Cho, H. J. Lee, W. I. Oh, and Y. K. Kim, 94th ASM Gen. Meet., abstr. E-44, 1997). In the group assayed here, the decrease in serum sCD8 (27.4%) was even greater than those observed previously (13.8 and 19.2%) and greatly differed from the rebound phenomenon observed during zidovudine monotherapy. Thus, the decrease in serum sCD8 may be indicative of a lower level of destruction of CD8 T cells in patients ingesting KRG and suggests that KRG intake is associated with prolonged maintenance of enhanced CD8 T lymphocyte activity.

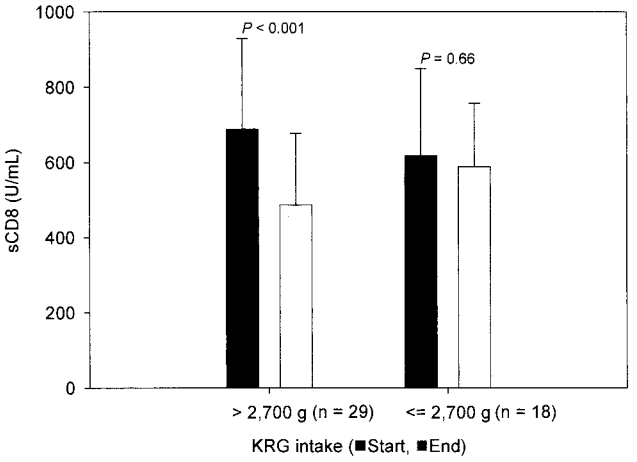

FIG. 4. Effects of KRG intake on serum sCD8 irrespective of HLA score. Forty-seven patients were divided into two groups based only on the amounts of KRG intake. The first level indicates averages of first measurements of sCD8, and the end level indicates averages of last measurements of sCD8 of this study. The statistical significance was calculated by a Student's two-tailed t test for two groups.

Although the mechanism of ginseng is not well understood, it is demonstrated that the adaptogenic properties of ginseng are due to its effects on the hypothalamic-pituitary-adrenal axis, resulting in elevated plasma corticotropin and corticosteroid levels (11, 14, 25). This action of ginseng might contribute a lot for suppressing hyperactivation of immune systems. The important role of suppressing the hyperimmune state in preventing AIDS progression was recently demonstrated by a study demonstrating that nonpathogenic simian immunodeficiency virus infection of sooty mangabeys is characterized by low-level immune activation despite chronic high-level viremia compared to other species of monkey, leading to AIDS progression (30). Intake of KRG may be associated with a continuous supply of corticosteroid hormone without side effects as well as maintaining prolonged CD8 T lymphocyte activity by less destruction of CD8 T cells, suggesting maintenance of balance in the immune system.

Despite the enormous efforts for decades aimed at developing AIDS vaccines, effective vaccines against HIV are not available yet. Considering the extreme difficulties involved in developing HIV vaccines and the limitations of HAART chemotherapy, KRG intake provides an alternative and effective way of treatment for HIV-infected patients.

In conclusion, these data show that KRG intake independently has beneficial effects on the slow decrease in CD4 T cells and on serum sCD8 levels in HIV-1-infected patients, although the HLA factor was also significantly associated with the rate of CD4 T cell depletion in the Korean population.

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