



Research article

Effect of Korean Red Ginseng intake on the survival duration of human immunodeficiency virus type 1 patients



Young-Keol Cho*, Jung-Eun Kim

Department of Microbiology, University of Ulsan College of Medicine, Seoul, Korea

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ABSTRACT

Background: Long-term ginseng intake can increase longevity in healthy individuals. Here, we examined if long-term treatment with *Panax ginseng* Meyer (Korean Red Ginseng, KRG) can also enhance survival duration (SD) in patients with human immunodeficiency virus type 1 (HIV-1) infection.

Methods: We retrospectively analyzed 252 HIV-1 patients diagnosed from 1986 to 2013 prior to the initiation of antiretroviral therapy. Overall, 162 patients were treated with KRG (3,947 ± 4,943 g) for 86 ± 63 mo. The effects of KRG on SD were analyzed according to the KRG intake level and the length of the follow-up period.

Results: There were significant correlations between the total amount of KRG and SD in the KRG intake group ($r = 0.64, p < 0.0001$) as well as between total amount of KRG and mean annual decrease in CD4⁺ T-cell count in all 252 patients ($r = -0.17, p < 0.01$). The annual decrease in CD4⁺ T-cell count (change in cells/μL) was significantly slower in KRG-treated patients than in patients receiving no KRG (48 ± 40 vs. 106 ± 162; $p < 0.001$). The SD (in months) was also significantly longer in the KRG group than in the no-KRG group (101 ± 64 vs. 59 ± 40, $p < 0.01$).

Conclusion: KRG prolongs survival in HIV-1 patients, possibly by slowing the decrease in CD4⁺ T-cell count.

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1. Introduction

Progressive loss of CD4⁺ T cells is the hallmark of human immunodeficiency virus (HIV) infection, and is accompanied by chronic inflammation and chronic immune hyperactivation [1]. In HIV patients, CD4⁺ T cells gradually and persistently decrease from the normal level of 800–1,200/μL to 0/μL. Untreated patients die, on average, 11 yr after primary infection [2], but the introduction of highly active antiretroviral therapy (HAART) in 1996 has markedly reduced the rates of mortality and morbidity [3]. It is currently recommended that individuals infected with human immunodeficiency virus type 1 (HIV-1) be initiated on a combination of at least three antiretroviral agents, even in the early symptomatic stages [4]. However, persistent HIV-1 replication maintains the tissue reservoir during therapy [5], and long-term HAART causes many side effects and ultimately results in drug resistance with ensuing therapeutic failure [6]. Thus, alternative and adjuvant therapies may be needed as these patients age.

Several host and viral factors are known to affect the rate of disease progression [7,8]. For instance, polymorphisms in the human leukocyte antigen (HLA) and C–C chemokine receptor type 5 (CCR5) are important host variables that affect disease progression [9]. However, the 32-bp deletion in the CCR5 gene (CCR5-Δ32) that is known to protect against infection has not been found in the Korean population [10]. However, we have shown significant inverse correlations between the HLA prognostic score and the annual decrease in CD4⁺ T cells (AD) [11], as well as between Korean Red Ginseng (KRG) intake and RNA copy number [12]. Thus, KRG may slow disease progression in vulnerable populations.

Panax ginseng Meyer has long been used as a general tonic for promoting longevity in the Far East, especially in China, Korea, and Japan [13]. *P. ginseng* is well known as an adaptogenic agent that increases physical performance, vitality, resistance to stress, and immunomodulatory activity [14–17]. *P. ginseng* contains a series of ginsenosides, acid polysaccharides, and many trace elements [13]. Recently, the anti-inflammatory efficacy of ginseng and adjuvant

* Corresponding author. Department of Microbiology, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
 E-mail address: ykcho2@amc.seoul.kr (Y.-K. Cho).

activities of saponins have been demonstrated in animal models of inflammatory disease [18–21]. We are conducting a long-term series of studies on KRG, either alone or in combination with zidovudine or HAART, for the treatment of HIV-1 infection [10,11,22–28], and have documented significant benefits.

It is well known that the long-term intake of ginseng promotes longevity, as described in books on traditional medicine [13]. However, no previous report has described the long-term outcomes in a cohort treated with ginseng for a specific disease such as AIDS. Therefore, our ginseng AIDS cohort may be a good model to evaluate the historical hypotheses regarding the benefits of ginseng.

In our present study, we retrospectively analyzed the AD and survival duration (SD) of an AIDS cohort to determine whether KRG treatment improves the immune function and longevity of HIV-1 patients. Furthermore, this study was limited to the period prior to the initiation of HAART for each patient. Our data indicate that long-term treatment with KRG increases longevity in HIV-1 patients.

2. Materials and methods

2.1. Study population

This study included 252 HIV-1 patients whose CD4⁺ T-cell counts were available prior to HAART. Of these, 207 were diagnosed during 1986–1992, 19 in 1993, and 26 during 1994–2013. First, we divided the patients according to the monthly amount of KRG (mKRG) intake (0 g, ≤ 30 g, or > 30 g) and follow-up period (< 10 yr, *n* = 192, or > 10 yr, *n* = 60). This study was approved by the Institutional Review Board of Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

2.2. Treatment with KRG

Since November 1991, we have studied the effects of oral KRG (5.4 g/d; Korea Ginseng Corporation, Seoul, Korea) on patients with HIV-1 infection. We instructed patients to orally take six capsules (300 mg/capsule) three times daily [10,24]. There were several interruptions in KRG intake before 2001. The total amount of KRG (tKRG) supplied and yearly KRG intake in the 162 KRG-treated patients enrolled were 3,917 ± 4,972 g and 559 ± 435 g, respectively, over an interval of 86 ± 63 mo (Table 1).

Table 1
Effects of Korean Red Ginseng on CD4⁺ cell count and SD of HIV-1 patients

Item	Group		<i>p</i>
	Non-KRG patients	KRG patients	
No. of patients	90	162	
Male:female	86:4	142:21	
Age (yr)	32.5 ± 9.2	30.3 ± 9.6	>0.05
No. of dead patients	30	52	>0.05
Suicide	4	2	>0.05
KRG supplied (g)	0	3,947 ± 4,943	
Range (g)	0	30–25,602	
Yearly KRG (g) ¹⁾	0	575 ± 474	
Baseline CD4 ⁺ T cells (/ μ L)	539 ± 301	508 ± 239	>0.05
Last CD4 ⁺ T cells (/ μ L)	302 ± 244	232 ± 223	<0.05
Interval (mo)	40 ± 32	85 ± 63	<0.001
AD (/ μ L)	106 ± 162	48 ± 40	<0.001
SD (mo)	59 ± 40	101 ± 64	<0.001
Survivor for > 10 yr	8	52	<0.001
Survivor for > 15 yr	1	14	<0.05

AD, annual decrease of CD4⁺ T cells; HIV-1, human immunodeficiency virus type 1; KRG, Korean Red Ginseng; SD, survival duration

¹⁾ For the interval between the baseline CD4⁺ T-cell count and the last CD4⁺ T-cell count

2.3. CD4⁺ and CD8⁺ T-cell measurements

After staining peripheral blood mononuclear cells with phycoerythrin- and fluorescein isothiocyanate-conjugated antibodies raised against the CD4 and CD8 antigens (Simultest reagent; Becton Dickinson, San Jose, CA, USA), CD4⁺ and CD8⁺ T cells were counted using a FACScan flow cytometer (Becton Dickinson) at 6-mo intervals [9,22,23].

2.4. Definitions of CD4⁺ T-cell count interval and SD

The CD4⁺ T-cell count interval was defined from the first to the last CD4⁺ T-cell measurement prior to HAART. SD (or follow-up period) was defined as the period between the diagnosis of HIV-1 infection and the last CD4⁺ T-cell count measurement prior to HAART. Oral KRG was initiated after the first CD4⁺ T-cell measurement. Hence, the duration of KRG intake was shorter than the defined CD4⁺ T-cell count interval.

2.5. Statistical analysis

All data were expressed as mean ± standard deviation. Differences in categorical data were tested using the Chi-square test for paired groups or Fisher's exact test for multiple (3) groups. Correlation strength between the amount of KRG, and both SD and AD was tested by Pearson's coefficients. All statistical analyses were performed using SPSS package version 12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. KRG slows CD4⁺ T-cell count reduction and prolongs survival of HIV-1 patients

The 252 study patients consisted of 162 KRG-treated and 90 untreated (non-KRG) patients. There were no differences in the mean age, mortality, or suicide rate between groups. Furthermore, baseline CD4⁺ T-cell count did not differ (Table 1). However, the yearly rate of CD4⁺ T-cell decrease (AD) was significantly slower in patients of the KRG group than in those of the non-KRG group (*p* < 0.001; Table 1). Consistent with the slower fall in CD4⁺ T-cell count, SD was also significantly longer in the KRG group. We found no significant difference in AD (in μ L) and SD (in months) between patients receiving a lower monthly dose of KRG (≤ 30 g, 15.5 ± 8 g/mo) and those receiving a higher dose (> 30 g, 68 ± 32 g/mo) (AD: 57 ± 70 vs. 43 ± 79, SD: 94 ± 48 vs. 106 ± 73). There was, however, a significant difference in SD between the groups receiving 0 g (106 ± 163/ μ L in AD and 59 ± 40 mo) and ≤ 30 g of KRG (54 ± 69/ μ L in AD and 94 ± 48 mo). The proportions of survivors beyond 10 yr and 15 yr were significantly higher among the KRG-treated patients (*p* < 0.01; Table 1).

We also analyzed the effects of KRG intake and follow-up period on SD among the 252 study patients. We first divided the patients according to the mKRG intake (0 g, ≤ 30 g, or > 30 g). The AD rates in mKRG ≤ 30 g and mKRG > 30 g groups were significantly slower than those in the non-KRG (0 g) group (*p* < 0.05 and *p* < 0.01, respectively; Fig. 1A). Hence, SD was significantly prolonged in patients receiving any dose of KRG (*p* < 0.001, Fig. 1B). Compared with the non-KRG group, SD was significantly higher in the mKRG ≤ 30 g and mKRG > 30 g groups.

3.2. Effect of KRG on AD

The cumulative dose depends on the total follow-up period; therefore, we also divided patients into two groups according to

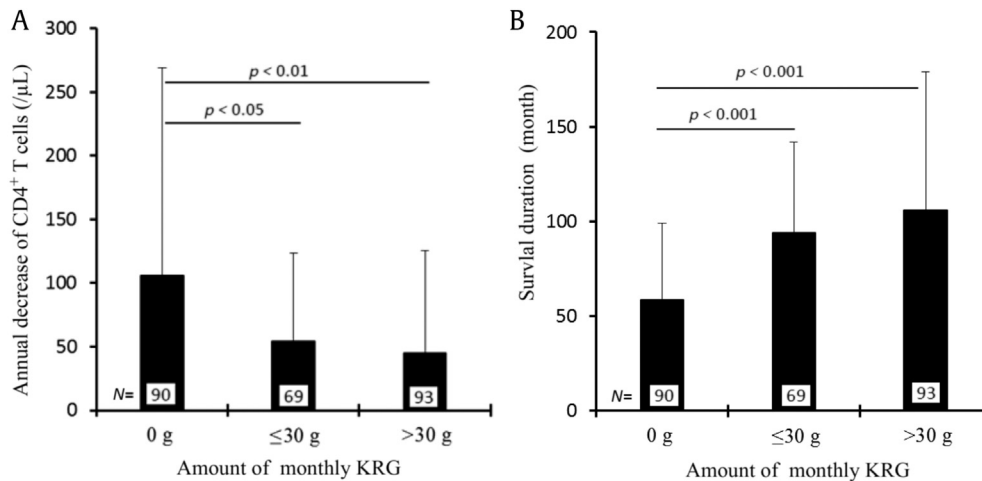


Fig. 1. AD and SD in HIV-1 patients according to the mKRG intake. (A) AD was significantly slower in the two groups with mKRG intake of ≤ 30 g (15.5 ± 8 g) and > 30 g (68.1 ± 32 g) than in patients with no KRG intake. (B) SD was significantly prolonged in the two groups that received KRG (≤ 30 g and > 30 g) compared with the group that did not receive KRG. Despite a significant difference in mKRG intake ($p < 0.0001$), there were no significant differences in AD and SD between the mKRG ≤ 30 g and mKRG > 30 g groups. AD, annual decrease of CD4⁺ T cells; KRG, Korean Red Ginseng; mKRG, monthly amount of Korean Red Ginseng; SD, survival duration.

follow-up for > 10 yr and ≤ 10 yr, and then compared the effects of mKRG intake ($0\text{--}30$ g or > 30 g; Fig. 2). The AD in patients with a follow-up period of ≤ 10 yr was markedly faster than in those followed up for > 10 yr (80 ± 131 cells/ μL for 46 ± 30 mo vs. 39 ± 42 cells/ μL for 146 ± 61 mo; Table 2). We also divided these patients into two groups according to mKRG intake (a ≤ 30 g group receiving 6.3 ± 9.9 g/mo and a > 30 g group receiving 70.5 ± 31 g/mo). The tKRG intake in patients with a follow-up period of > 10 yr was significantly higher than in those with a follow-up period of ≤ 10 yr (Fig. 2A). In patients with a follow-up period of < 10 yr, the AD was significantly faster in the group with mKRG $0\text{--}30$ g than in the group with mKRG > 30 g (91 ± 145 vs. 54 ± 94 , $p < 0.05$; Fig. 2B). In patients with a follow-up period of > 10 yr, the SD in the mKRG > 30 g group was significantly improved compared with those with an mKRG intake of $0\text{--}30$ g (193 ± 57 vs. 148 ± 26 , $p < 0.0001$; Fig. 2C).

There were also a mild significant difference in AD between the 81 untreated patients and the 48 patients treated with mKRG ≤ 30 g (108 ± 171 vs. 62 ± 80 , $p = 0.081$) and a significant difference in SD (50 ± 31 vs. 69 ± 31 , $p < 0.01$). However, there was no significant difference in SD between the mKRG ≤ 30 g and mKRG > 30 g groups (69 ± 31 vs. 65 ± 34).

The AD of patients with a follow-up period of > 10 yr ($n = 60$) was 39 ± 42 cells/ μL for 146 ± 61 mo. The SD in these cases was 172 ± 49 mo, although the age at diagnosis was significantly less than in the ≤ 10 yr follow-up group (Table 2). We divided these 60 patients into two groups according to the mKRG intake ($0\text{--}30$ g vs. > 30 g; Table 3), and found significantly slower AD and longer SD ($p < 0.001$) in the mKRG > 30 g group (Figs. 2B and 2C, Table 3).

When we further divided the 30 patients with $0\text{--}30$ g mKRG intake into mKRG = 0 g and mKRG ≤ 30 g groups, there was a significant difference in AD (89 ± 74 cells/ μL in the 9 untreated patients vs. 37 ± 29 cells/ μL in the mKRG ≤ 30 g group, $p < 0.01$), but no significant difference in SD (141 ± 25 vs. 151 ± 26). There was, however, a significant difference in SD between mKRG ≤ 30 g and mKRG > 30 g patients (151 ± 26 vs. 193 ± 57 , $p < 0.01$).

3.3. Overall effects of KRG

We analyzed the effect of KRG intake on SD in all 252 patients. The 162 KRG-treated patients were supplied with 575 ± 474 g/yr for 85 ± 63 mo (Table 1). There were significant correlations

between mKRG and both AD ($r = -0.1741$, $p < 0.01$) and SD ($r = 0.1865$, $p < 0.01$). Furthermore, significant correlations were observed between tKRG and SD ($r = 0.6390$, $p < 0.0001$) and between tKRG and AD ($r = -0.173$, $p < 0.01$). In contrast to the mKRG intake, the correlation between tKRG and SD was also significant in the 162 patients receiving KRG ($r = 0.6433$, $p < 0.0001$; Fig. 3).

4. Discussion

The World Health Organization recommends early and life-long HAART treatment for HIV-1 patients [4]. However, HAART has a number of limitations. Considering the long-term side effects of HAART and the possible development of drug resistance, alternatives and adjuncts are urgently required. Our long-term follow-up of AIDS patients prior to HAART suggests that KRG treatment is an effective alternative or adjunct, although its efficacy is not broadly recognized for AIDS therapy.

Introduction of HAART is recommended when the CD4⁺ T-cell count falls to $200\text{--}350/\mu\text{L}$. In most of our present study patients, introduction of HAART was delayed by poor compliance or patient reluctance due to its toxicity or side effects, and by the lack of supply (a problem up to the early 2000s). Ginseng has been shown to promote longevity in the healthy population (hazard ratio = 0.90 in male ginseng users [29]) and may slow the progression of other diseases. To date, however, there have been no reports on the association between ginseng intake and survival in HIV. We found that long-term KRG intake indeed prolonged the SD of HIV-1 patients prior to HAART.

It is well known that HIV-1-specific CD8⁺ T cells from viral controllers contain more granzyme B and perforin, and release a larger amount of interferon- γ than cells from HIV progressors [30]. It is possible that the benefits of ginseng are mediated in part by its effects on CD8⁺ T cells. A recent report found an increased mRNA expression of interferon- γ , granzyme B, and Fas ligand in KRG-treated Balb/c mouse infected with herpes simplex virus [31]. In addition, we reported that the decrease in soluble CD8 antigen in serum was higher in HIV-1 patients taking KRG [11,32] and that this decrease in soluble CD8 antigen was maintained as long as KRG was taken. We, thus, speculate that the cytotoxic T-lymphocyte activity may be potentiated in HIV-1 patients by KRG treatment [26,27], resulting in an increased SD.

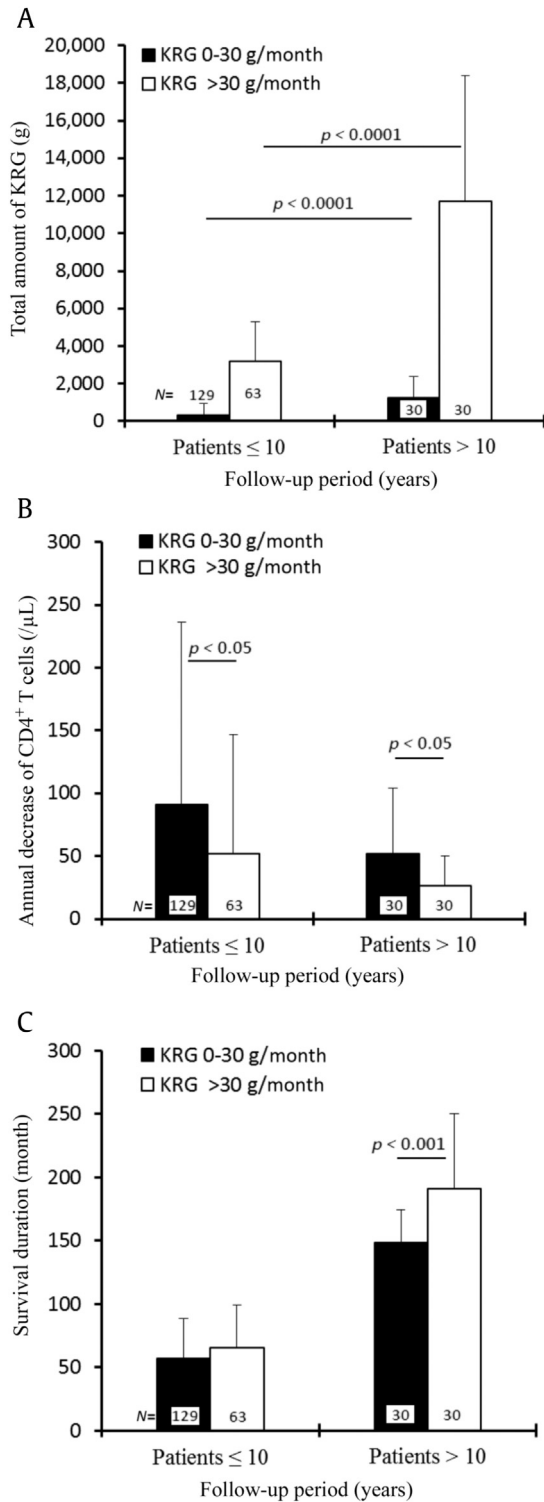


Fig. 2. AD and SD in HIV-1 patients according to the mKRG intake by follow-up period (≤ 10 yr or > 10 yr). (A) The total KRG intake was significantly higher in patients with a follow-up period of > 10 yr. In patients with follow-up periods of > 10 yr and ≤ 10 yr, (B) AD was significantly faster in the lower KRG intake group and (C) SD was prolonged in the higher KRG intake group. AD, annual decrease of CD4⁺ T cells; KRG, Korean Red Ginseng; mKRG, monthly amount of Korean Red Ginseng; SD, survival duration.

One notable limitation of this study is that guidelines for the initiation of HAART were not strictly applied to all patients because of the lack of cooperation/compliance and drug availability, although all our patients were recommended to follow the

Table 2
Effect of KRG on the annual decrease in CD4⁺ T cells by follow-up period

Item	Follow-up period		p
	≤10 yr	>10 yr	
No. of patients	192	60	
Male:female	180:12	47:13	<0.01
Age (yr)	33 ± 9	27 ± 10	<0.001
KRG supplied (g)	1,280 ± 1,865	6,728 ± 7,097	<0.001
Range (g)	0–12,960	0–25,602	
Monthly KRG (g)	28 ± 36	41 ± 40	<0.05
Baseline CD4 ⁺ T cells (μL)	488 ± 251	601 ± 275	<0.01
Last CD4 ⁺ T cells (μL)	262 ± 232	233 ± 206	>0.05
Interval (mo)	46 ± 30	146 ± 61	<0.0001
AD (μL)	80 ± 131	39 ± 42	<0.05
SD (mo)	60 ± 33	172 ± 49	<0.0001

AD, annual decrease of CD4⁺ T cells; KRG, Korean Red Ginseng; SD, survival duration

Table 3
Effect of KRG intake level on SD of HIV-1 patients followed up for more than 10 yr

Item	Monthly KRG intake		p
	0–30 g	>30 g	
No. of patients	30	30	
Male:female	25:5	22:8	>0.05
Age (yr)	24 ± 10	26 ± 6	>0.05
KRG supplied (g)	1,258 ± 1,144	11,704 ± 6,672	<0.001
Range (g)	0–3,900	3,258–25,602	<0.001
Monthly KRG (g)	10 ± 9	67 ± 34	<0.001
Baseline CD4 ⁺ T cells (μL)	643 ± 324	575 ± 215	>0.05
Last CD4 ⁺ T cells (μL)	222 ± 189	231 ± 224	>0.05
Interval (mo)	115 ± 39	176 ± 64	<0.001
AD (μL)	52 ± 52	26 ± 24	<0.05
SD (mo)	148 ± 26	193 ± 57	<0.001
Survivor for >15 yr	4	12	<0.05
No. of dead patients	11	3	<0.05

AD, annual decrease of CD4⁺ T cells; HIV-1, human immunodeficiency virus type 1; KRG, Korean Red Ginseng; SD, survival duration

guidelines for the initiation of HAART [33]. In addition, the patient group was heterogeneous, with a high proportion of overseas sailors (data not shown). Demographic and lifestyle factors such as education, occupation, alcohol drinking, smoking, and socioeconomic status should be considered when evaluating future HIV-1 cohorts. Despite these limitations, our study shows that even moderate KRG doses for a sufficient period can improve SD in HIV-1 patients not receiving HAART and that efficacy improves with cumulative intake.

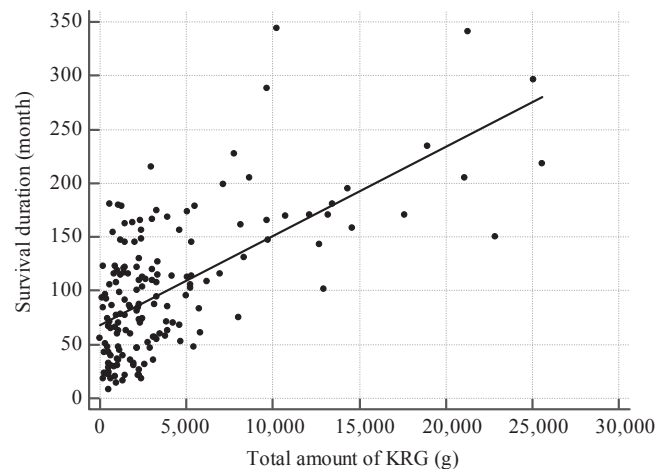


Fig. 3. Correlation between the total amount of KRG consumed and survival duration (months) in the 162 KRG group patients ($r = 0.64$, $p < 0.0001$). KRG, Korean Red Ginseng.

Better-designed and larger-scale studies should focus on HIV-1 subtype differences and ginseng-based combination therapies.

Conflicts of interest

None declared.

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