International Journal of Medicinal Plants and Alternative Medicine Vol. 4(1), pp. 001-004, October 2016
Available online at http://academeresearchjournals.org/journal/ijmpam
ISSN 2327-560X ©2016 Academe Research Journals

Review

Daily dietary administration of a proprietary extract of North American ginseng results in progressive, transient but significant body weight gains in normal, elderly mice

Durairaj Punithavathi and Miller Sandra C*.

Department of Anatomy and Cell Biology, McGill University, 36 40 University St., Montreal, Quebec, Canada H3A 0C7.

Accepted 3 October, 2016

We have administered i*n vivo*, a proprietary extract of North American ginseng (CVT-E002) to elderly (18 months) normal C3H mice for 8 months at which time half were converted to the control diet for another 3.5 months. Control mice were identical in every way, except their diet contained no CVT-E002. Body weights (b.w.), recorded weekly, revealed a progressive increase throughout the first 6 months, reaching a maximum and plateauing thereafter in spite of continued CVT-E002. Withdrawal of CVT-E002 resulted in a progressive decrease in b.w. toward control levels during the subsequent 3.5 months. The transient, CVT-E002-dependency of the b.w. increments negates the possibility of metabolic disease induction by this extract.

Key words: North American ginseng, body weights, elderly mice.

INTRODUCTION

We have previously observed the effect of a proprietary extract (Afexa Life Sciences, Inc., Edmonton, Alberta, Canada) of North American ginseng (*Panax quinquefolium*), that is, CVT-E002, on the body weights of mice in assorted states of health and disease, both genders, different ages and strains of laboratory mice.CVT-E002 consists of specific polysaccharides (poly-furanosyl-pyranosyl-saccharides) and standard chemical and biological assays have been applied together with consistent manufacturing processes to ensure that both the pharmacological activity and composition of all preparations of CVT-E002 are identical.

We have shown that in young adult CD-1 male and female mice, injected daily with CVT-E002 in infancy (1 wk of age) for 14 days, their body weights,upon reaching young adulthood (8 wk of age) were 10% greater than the body weights of the corresponding, uninjected control mice (Miller and Delorme, 2008). Secondly, when leukemic infant,(1 wk of age) DBA/2 mice were given daily injections of CVT-E002 at 20mg/day, for 14 days and weighed daily throughout this period, their body weights from day 5 onward were significantly higher ($p < 0.01$-0.001) than in mice injected with 30, 40, or 50 mg/day (Miller, Delorme and Shan, 2011). This study, together with another in adult tumor-bearing mice (Miller, Delorme and Shan, 2009) revealed the dose of CVT-E002 is an important feature when assessing all parameters, including body weight, after administering CVT-E002. Third, female mice of the C3H/HeN strain (22 months of age) were fed daily CVT-E002 for 48 week. Within the first 8 week, body weights in the CVT-E002-fed mice increased only insignificantly, however between 12 and 32 week they increased to significant levels relative to identical control mice. However from 32 week until 48 week, body weights plateaued, when the study concluded (Durairaj and Miller, 2012a). Fourth, to young,

*Corresponding author. E-mail: sandra.miller@mcgill.ca. Tel: 514-398-6358. Fax: 514-398-5047.

adult male mice (7 weeks of age) of the C3H/HeN strain, we injected a carcinogen which, by 50 week of age, in control mice, led to 100% development of hepatoma with all the control mice dying by 82 week (Durairaj and Miller, 2012b). For all mice, body weights were recorded weekly. In CVT-E002-fed mice, by 16 wk after beginning daily feeding, body weights were significantly elevated, reaching a peak at 16 week after which they plateaued in spite of continued daily feeding of CVT-E002 (Durairaj and Miller, 2012b). Although all CVT-E002 mice remained alive, this study was concluded at 82 wk with the death of the last control animal.

Based on all these recent studies, it is apparent that irrespective of health status, age, gender or genetic diversity (different mouse strains), the positive effect mediated by CVT-E002 on body weight is consistent and may even be predictable.

CVT-E002 also has an effect on the cells of the immune system. It is a powerful immunity enhancer owing to its ability to stimulate several immune system-dependent cytokines, that is, IFN-y, Il-6, Il-1, nitric oxide (NO), and TNF-α (Wang et al., 2001, 2004; Shan et al., 2007). Not only are these factors pleiotrophic and have functions that are exquisitely dose and exposure-time-dependent, but 2 or more can act together to produce a given function. Regardless of specific mechanism, it has been shown that daily administration of CVT-E002 to cancer-prone mice (Durairaj and Miller, 2012a), to carcinogen-administered mice (Durairaj and Miller, 2012b), and to neoplasia-bearing mice (Miller, Delorme and Shan, 2009; Miller, Delorme and Shan, 2011), significantly reduces the existing cancer, or completely prevents it, significantly extending life span.

Given our consistent observations of body weight increases followed by weight plateaus, in our previous studies, in spite of continuing CVT-E002 administration, we hypothesized that if CVT-E002 was removed from the diet, body weights would return to normal, control levels. Our aim in the present study was to feed aged female mice (aged 18 months) CVT-E002, daily in the chow for several months and then withdraw it, returning the mice to the control diet for several more months. We used aged female mice to eliminate the possibility of hormonal influence on body weight which would be a confounding influence. Indeed, we found that in these aged, normal, mice, body weights not only increased in the presence of CVT-E002, but upon withdrawing CVT-E002 and placing them on the control diet, body weights progressively decreased back toward control levels, confirming our hypothesis.

RESULTS AND DISCUSSION

Virtually all mice (both genders) of the C3H strain are prone to alopecia (hair loss) to a greater or lesser extent in the latter stages of aging. This is a peculiarity of this strain, although it is also observed sporadically, in elderly mice of other strains and is not considered a disabling, pathological condition.Alopecic C3H mice behave normally,having a life span comparable to that of other strains.

Figure 1 demonstrates the progressive body weight changes, vs control, in mice of 18 months of age, placed on a daily diet containing CVT-E002. For the first month of daily feeding (0 - 4 week), there was a slight but insignificant increase in body weight, however this increase was gradual and became significant by 8 week, progressively increasing from 8 - 20 week after which a plateau was observed (20 - 32 week) in spite of continued CVT-E002 feeding.

We had, in a previous study using aged female C3H mice (Durairaj and Miller, 2012a) which were similar to the mice in the present study, carried out autopsy analyses of various organs after such mice had consumed of CVT-E002 for several months. Those results revealed subcutaneous thickenings as well as fat depositions around the internal viscera – phenomena not seen in autopsies of the parallel control mice. It is known that estrogen presence *in vivo* is related to lipid deposition and like many herbs, *P. quinquefolium* has phytoestrogenic properties (Duda et al., 1996; King et al., 2006).However, CVT-E002 is a specific extract of *P. quinquefolium*, containing only specific polysaccharides (poly-furanosyl-pyranosyl saccharides) having no known estrogenic properties.

Figure 2 continued the trend observed in Figure 1, in demonstrating that as daily feeding of CVT-E002 continued beyond 32 week (Figure 1), up to 46 week, there was no further increase in body weight after that observed at 20 week (Figure 1). Figure 2 also demonstrates another phenomenon, novel to the present study. That is, body weights in CVT-E002-fed mice declined progressively toward control levels after withdrawing CVT-E002 from the diet. In spite of removing CVT-E002 from the diet (week 32: Figure 1), there was no apparent effect of this withdrawal when body weights were recorded at week 35 (Figure 2). However, a slow and progressive loss in body weight became perceptible at week 36 (Figure 2), continuing until week 42 when the weight reduction of mice in this “withdrawal” group became statistically significant relative to that of mice still consuming CVT-E002 ($p< 0.05$). This body weight reduction toward control levels, was even more significant ($p<0.001$) at 46 week. The body weights of all the control diet mice from 18 months of age (time 0: Figure 1), up until the conclusion of this study (46 wk: Figure 2) remained unchanged. At the conclusion of this study (46 week: Figure 2), all mice were aged 29.5 months, that is, 2 .5 year.

The fact that the body weights of the elderly mice in the present study had progressively decreased after withdrawing CVT-E002, suggested that these mice had not developed a physiological pathology, that is,

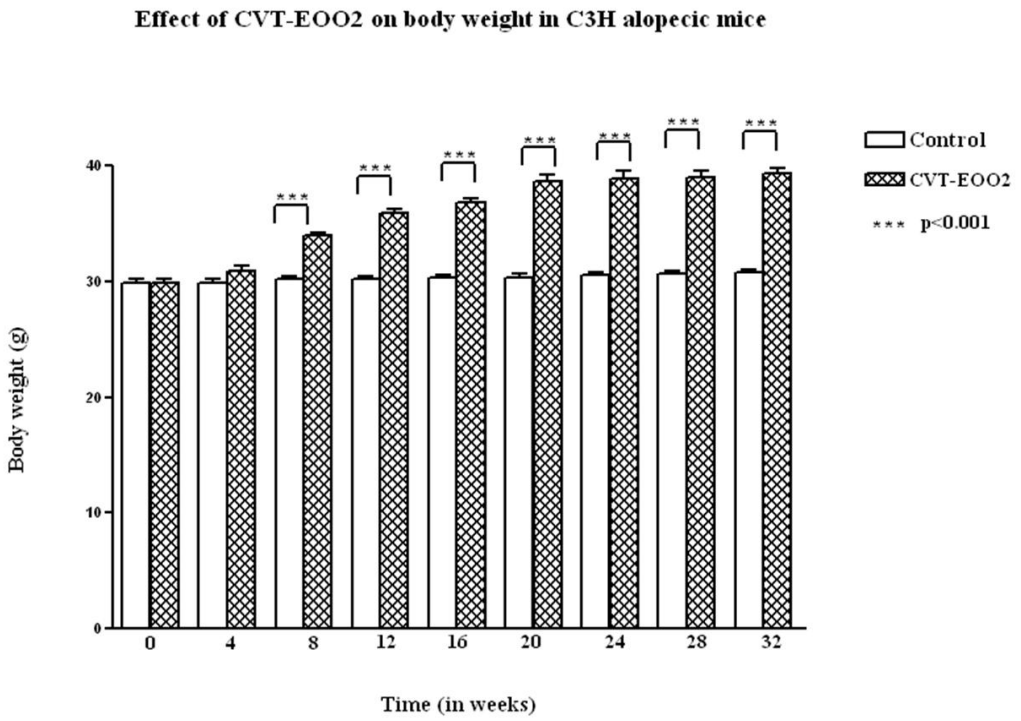

Figure 1: Elderly, alopecia C3H female mice (18 months) began receiving, at 18 months of age, 80 mg of CVT-E002, a proprietary extract (Afexa Life Sciences, Inc., Edmonton AB, Canada), of North American ginseng in 6 gm chow/day/mouse for 32 week (8 months) (N = 14). Both the dose of CVT-E002 and the precise quantity of chow consumed/adult mouse/day, had been well established previously in dose/response studies in our lab (Miller and Delorme, 2008; Miller, Delorme and Shan, 2009; 2011). Body weights were taken weekly from time 0, and were presented graphically at 4 wk intervals thereafter until mice were 26 months (18 + 8) of age, that is, >2 year. The data reveal a progressive and ultimately significant increase (8 - 32 week) in body weight. Control mice (N = 14) were identical in every aspect except that CVT-E002 was not present in the daily chow.

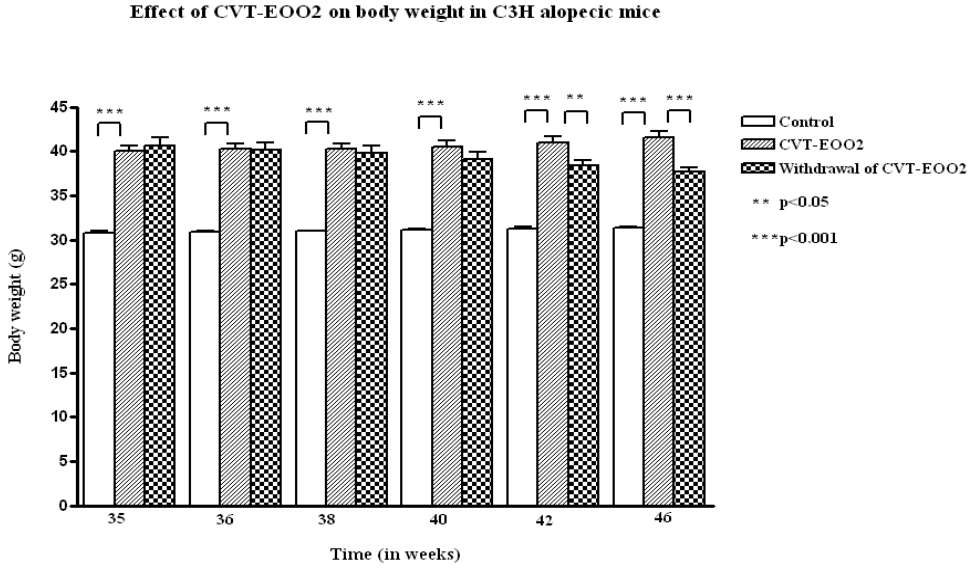

Figure 2: CVT-E002 was removed from the daily chow from half the mice (N = 7) of Figure 1 after 32 week (8 months) of daily feeding, and placed on the control diet until 46 week, while the remaining half (N = 7) continued to consume daily dietary CVT-E002 in parallel. Control mice were the same animals (N = 14) indicated in Figure 1, and continued on the same control diet regimen as they had been from time 0 (Figure 1).

metabolic syndrome (diabetes mellitus) even during the long period of availability of dietary CVT-E002. Although the precise mechanism by which this CVT-E002-induced, transient body weight augmentation occurred is unknown, what is known is the fact that CVT-E002 *in vivo*, results in the stimulation of a host of endogenous cytokines and growth factors,one of which is TNF-α. This endogenous factor is known to have wide-spread metabolic effects and is known to be involved in lipid metabolism (Hotamisligil et al., 1993; Kern et al., 1995; Hauner et al., 1995; Argiles et al., 1997; Chen et al., 2009; Bosnjak et al., 2012). Precisely how body weight augmentation occurs in the presence of CVT-E002 may only be answered in the biochemistry lab.It remains for future studies to establish how, or even if, TNF-α is involved in weight gains in the presence of CVT-E002. If so, is a combination of TNF-α with other CVT-E002-augmented cytokines necessary to produce this phenomenon? Moreover, is protein and/or carbohydrate metabolism affected during long-term administration of CVT-E002? Finally, it may be justifiably speculated that administering CVT-E002 to animals, potentially including humans, afflicted with muscle-wasting diseases, or during cancer-bearing–again, potentially including humans, may off-set the severe cachexia which accompanies these conditions.

ACKNOWLEDGEMENTS

This project was support financially by a grant from Afexa Life Sciences, Inc., Edmonton, Alberta, Canada. No employee of this company had any input into its experimental design, data analysis/interpretation, or preparation of this manuscript.

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