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# The Effects of Panax Ginseng on Streptozotocin-Induced Diabetic Rats: Meta Analysis

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**Abstract**

The present study was carried out to summarize the effect of ginseng in the experimental diabetic rats by meta-analysis related studies. The association measure to test effect of ginseng was the mean difference(MD) between group of rats induced streptozotocin(STZ) and group of rats induced STZ treated with ginseng about the considered effect factors. The level of FI, glucose and TG were significantly reduced($< 0.01$), and the level of glycogen was significantly increased by treatment with ginseng ($< 0.01$). After checking the indication of publication bias for the combined MDs by using the funnel plots, the anti-diabetic effects of ginseng is clearly presented in FI, glucose, TG and glycogen ($< 0.05$).

Keywords: Panax Ginseng, meta analysis, publication bias, trim and fill method.

## 1. Introduction

According to King *et al.* (1998), the number of people with diabetes of the world is about 150 million and this is likely to reach 300 million or more by the year 2025 (King *et al.*, 1998). Reasons for this rapid rise include sedentary lifestyle, consumption of energy rich diet, obesity, *etc.* (Yajnik, 2001). Plant drugs are frequently considered to be less toxic and free from side effects than synthetic ones (Pari and Umamaheswari, 2000). Many herbal medicines have been recommended for the treatment of diabetes (Marles and Fransworth, 1995; Alarcon-Aguilara *et al.*, 1998).

Panax ginseng is also called Asian or Korean ginseng and the herbal remedies referred to as ginseng are derived from the roots of several plants. It is well known that Panax ginseng may improve psychologic function, immune function and conditions associated with diabetes and the studies about anti-diabetic effect of ginseng are increased. As the number of the studies, it is necessary that the anti-diabetic effect of ginseng was investigated by combination of studies.

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Meta-analysis is a tool for summarizing the results of studies related research hypotheses. It has three steps; deciding the association measure for detecting difference between groups, summarizing the association measure in assumed model and identifying publication bias. The association measures in meta-analysis are the measure related effect extracted from the primary research such as the standardized mean difference, the mean difference, the risk difference and an odds ratio. The decided measure is combined using only within variation of studies on the assumption that the results are homogeneity and uniformly distributed, and then it is tested whether the homogeneity assumption is plausible. If the results are heterogeneity, the measure is recombined using within variation with the estimated between variation of studies. The former model is called the fixed effect model and the latter is the random effect model. Because significant results are more likely to be submitted or accepted than insignificant one and the combined estimate are calculated only published researches, the bias easily occurs in small number of studies and the bias is called the publication bias. If the publication bias is doubtable, the combined estimate is adjusted or the additional studies are required (Choi and Kook, 2007a; Sutton *et al.*, 2000).

The purpose of this study was to summarize the factors related to diabetic disease and to investigate the anti-diabetic effect of ginseng in experimental diabetic rats. The combined results of studies were summarized as the mean difference and the standard deviation about diabetic factors between the diabetic group and the diabetic group with supplemented ginseng.

## 2. Investigation of the Anti-Diabetic Effect of Ginseng

The studies used in this meta-analysis were searched on the ScienceDirect in English, the DBpia database, and the KISS(Koreanstudies Information Service System) in korean. The search keyword used were ginseng, panax and diabetes and the research was limited to experimental rat studies. About 50 studies were collected and 9 studies were finally selected after omitting some studies which show lack of information, such as no sample variance or no sample size. In each study, there were two groups; the control group of diabetic rats induced by streptozotocin(STZ), and the treated group of diabetic rats induced STZ with ginseng. The factors to investigate the anti-diabetic effect of ginseng were collected from studies as many as possible, if the factor was studied in at least 2 studies. The selected factors were free fatty acid(FFA), food intake(FI), glucose, insulin, serum total cholesterol(TC), serum total glyceride(TG) and liver glycogen(glycogen). Because the level of experiment in each study were various, the number of data about glucose is more 9. The unit of each factor was uniformly changed.

### 2.1. Association measure and models for combining

Since the mean difference between the control group and the treated group was used for test about anti-diabetic effect of ginseng, the association measure was decided as the mean difference(MD) of each factor; mean of the control group minus mean of the treated group. In fixed effect model, it is assumed that the effect measure in the study population has a single value $\theta$ and the association measure is estimated by using a variation within the study. The fixed effect estimator $\bar{d}$ is given by

$$\bar{d} = \sum_{i=1}^{k} d_i w_i \Big/ \sum_{i=1}^{k} w_i.$$

The weights that minimize the variance of $\bar{d}$ and hence are routinely used, are inversely proportional

to the conditional variance in each study. An estimate of variance of the pooled estimate $\bar{d}$, is given by the reciprocal of the sum of the weights, *i.e.*

$$\mathrm{Var}\left(\bar{d}\right) = \frac{1}{\sum_{i=1}^{k} w_i}.$$

The homogeneity was investigated by Cochran's $Q$ statistic. If the homogeneity is plausible, then the $Q$ statistic is a chi-square variable with degree of freedom $k-1$ and has a small value. So

$$Q = \sum_{i=1}^{k} \left(d_i - \bar{d}\right)^2 w_i \sim \chi^2_{(k-1)}.$$

If the homogeneity was accepted by Cochrans $Q$ test, the association measure is estimated by using a variation within the study in the fixed effect model. If the homogeneity was rejected, the combined MDs of studies were calculated in random effect model. The estimated component of variance due to inter-study variation in effect size, $\hat{\tau}^2$, is calculated as

$$\hat{\tau}^2 = \mathrm{Max}\left(0, \frac{Q-(k-1)}{\sum_{i=1}^{k} w_i - \left(\sum_{i=1}^{k} w_i^2\right) \Big/ \sum_{i=1}^{k} w_i}\right).$$

Adjusted weights $w_i^*$ for each of the studies may now be calculated as

$$w_i^* = \frac{1}{\left(\frac{1}{w_i}\right) + \hat{\tau}^2}.$$

Thus the random effects study weighting is given by the reciprocal of the sum of the between and within study variances. The random effect estimator $\bar{d}^*$ can be computed by

$$\bar{d}^* = \frac{\sum_{i=1}^{k} d_i w_i^*}{\sum_{i=1}^{k} w_i^*}.$$

The variance of this estimate is simply

$$\mathrm{Var}\left(\bar{d}_i^*\right) = \frac{1}{\sum_{i=1}^{k} w_i^*}.$$

### 2.2. Identification the publication bias

Publication bias was identified by using a funnel plot and Eggers linear regression test. The funnel plot was a graph that the calculated association measures of studies about each factor, the MD in our study, were plotted against the inverse of the estimated standard error(SE) of them. The results from smaller studies will be more widely spread around the combined MD because of larger random

**Table 3.1.** Combined MDs and Homogeneity test in fixed effect model and random effect model

| | Fixed effect estimate | | Heterogeneity | Random effect estimate | |
|---|---|---|---|---|---|
| | estimate | $p$-value | $p$-value | estimate | $p$-value |
| FFA | −41.358 | 0.081 | < 0.001 | −69.985 | 0.169 |
| FI | −9.424 | < 0.001 | < 0.001 | −12.166 | < 0.001 |
| Glucose | −262.262 | < 0.001 | < 0.001 | −214.247 | < 0.001 |
| Insulin | 228.101 | < 0.001 | 0.004 | 212.001 | < 0.001 |
| TC | −8.042 | 0.164 | 0.212 | −11.173 | 0.158 |
| TG | −55.800 | < 0.001 | 0.313 | −55.100 | < 0.001 |
| Glycogen | 7.445 | < 0.001 | 0.874 | 7.445 | < 0.001 |

error. Therefore, the publication bias was doubtable if the shape of plot is funnel or cone around the combined MD. Eggers linear regression test was used to test the null hypothesis that funnel plot was not asymmetry. Eggers linear regression is a linear regression of standard normal deviate (defined as association measure over SE) against the inverse of SE and there may be publication bias if the estimated intercept is significantly different from 0. A positive intercept indicates that more studies are associated with bigger effect (Choi and Kook, 2007b; Whitehead, 2002).

If the publication bias is doubtable, the additional analysis is needed like trim and fill method. The trim and fill method provides estimate combined effect sizes after 2 steps process, in which the asymmetric data is trimmed and imputed. The trim and fill estimator is calculated in fixed effect model or in random effect model. The trim and fill method is used to compare the original estimates.

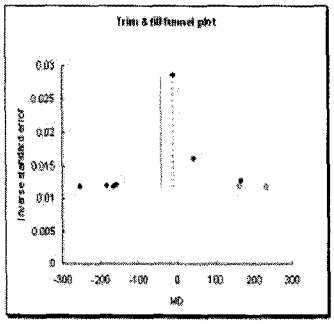
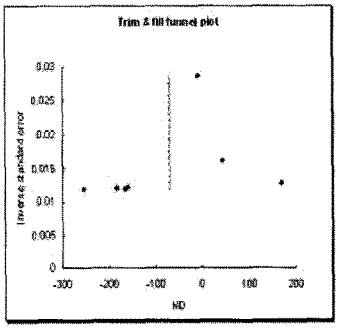
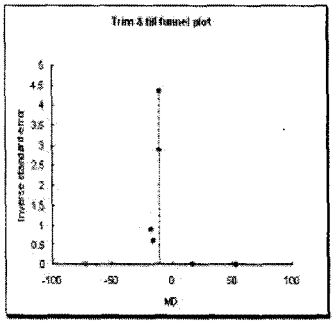
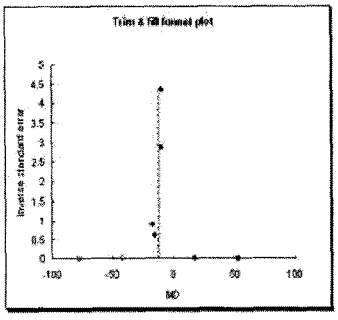
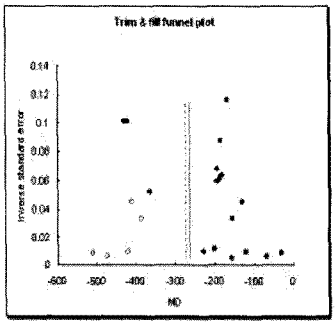
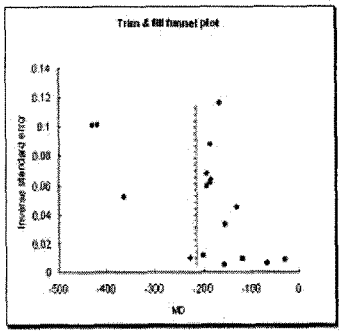
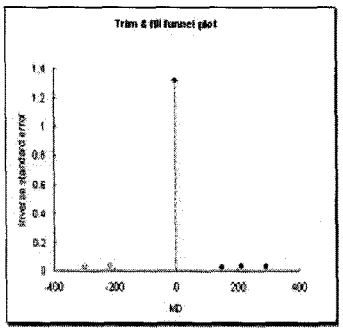
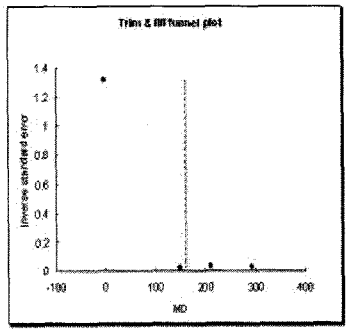
## 3. Investigation of Anti-Diabetic Effect

In Table 3.1, there are the combined MDs by the inverse variance weighted method and $p$-values to test the hypothesis H0: MD = 0 in the fixed effect model and in random effect model with $p$-value about test the hypothesis H0: Heterogeneity among primary studies. In Figure 3.1, the trim and fill funnel plots of effect factors were presented. The intercepts and $p$-value of Eggers linear regression test were presented to checking the publication bias in Table 3.2 and the fixed effect estimate and random effect estimate by trim and fill method were presented in Table 3.3.

### 3.1. The combined mean difference for diabetic factors

The considered factors were FFA, FI, glucose, insulin, TC, TG and glycogen. In fixed effect model, the anti-diabetic effect of ginseng to FFA and TC were not significant ($> 0.05$) and FI, glucose, insulin, TG and glycogen were significant ($< 0.05$). The $p$-values of heterogeneity test among studies about FFA, FI, glucose and insulin were less than 0.05, and TC, TG and glycogen were more. In random effect model, the effect of ginseng to FFA, and TC were not significant ($> 0.05$), and FI, glucose, insulin, TG and glycogen were significant ($< 0.05$). The mean differences of FFA, FI, glucose and insulin between RD and RDG were estimated by random effect model because of heterogeneity among studies. Because the between variation was estimated zero, the mean differences of TC, TG and glycogen were estimated by fixed effect model and had same value.

By upper reasons mentioned, the levels of FI, glucose and TG were significantly reduced ($< 0.01$), and the level of insulin and glycogen were increased by treatment with ginseng ($< 0.01$). The mean

| | Fixed effect model | Random effect model |
|---|---|---|
| FFA |  |  |
| FI |  |  |
| Glucose |  |  |
| Insulin |  |  |

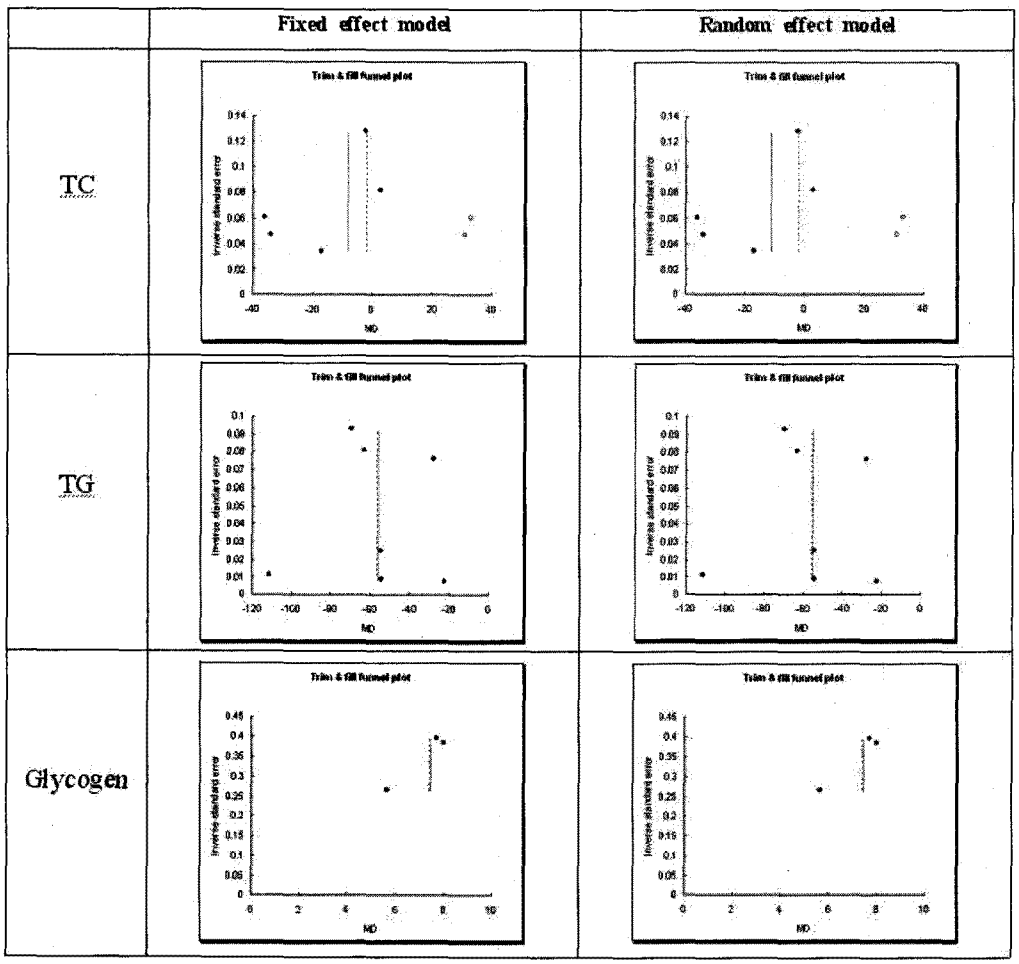



**Figure 3.1.** Funnel plot about factors related to ginseng

of FFA and TC of diabetic rats were not significantly different with them of diabetic rats with ginseng ($> 0.05$).

### 3.2. Checking the publication bias and recalculating the MD by trim and fill method

The MD estimates about FFA, FI, glucose, insulin and TC in Table 3.1 probably have the publication bias, because the dotted plots in funnel plot about them did not look like funnel or cone. In Figure 3.1, the circles in funnel plots of each factor mean the asymmetric data about the combined MD in Table 3.1. On the other hand, the intercepts of Eggers linear regression in Table 3.2 were not significantly different with 0 and the results of Egger's test mean the no publication bias.

We assumed the publication bias about the combined MD and then the MD estimates were recalculated by trim and fill method in Table 3.3. By trim and fill method in random effect model, the 95% confidence interval of mean difference about FFA, FI, glucose and insulin were ($-169.759$,

**Table 3.2.** Estimated intercepts and $p$-values of Eggers linear regression test

| | Publication bias | |
|---|---|---|
| | Intercept est. | $p$-value |
| FFA | −2.219 | 0.323 |
| FI | −2.287 | 0.306 |
| Glucose | 2.552 | 0.416 |
| Insulin | −2.806 | 0.232 |
| TC | −1.751 | 0.202 |
| TG | 0.021 | 0.978 |
| Glycogen | −1.728 | 0.148 |

**Table 3.3.** The 95% confidence interval of recombined Mean Difference

| | Fixed effect estimate | | Random effect estimate | |
|---|---|---|---|---|
| | CI_low | CI_up | CI_low | CI_up |
| FFA | −51.968 | 77.424 | −169.759 | 129.565 |
| FI | −9.793 | −8.685 | −14.468 | −7.602 |
| Glucose | −276.830 | −254.051 | −279.979 | −82.783 |
| Insulin | 211.271 | 283.467 | 146.303 | 356.791 |
| TC | −11.770 | 19.276 | - | - |

129.565), (−14.468, −7.602), (−279.979, −82.783) and (146.303, 356.791). That mean that the effect of ginseng about FI, glucose and insulin were significant ($< 0.05$). By trim and fill method in fixed effect model, the 95% confidence interval of mean difference about TC was (−11.770, 19.276), thus the effect of ginseng about TC was not significant ($> 0.05$).

Although the publication biases of estimated MDs between RD and RDG about FI, glucose and insulin are doubtable, the anti-diabetic effect of ginseng about them was significant.

## 4. Conclusion

This study investigated the anti-diabetic effect of ginseng about the level of FFA, FI, glucose, insulin, TC, TG and glycogen by meta analysis. The association measure is the mean differences between the diabetic rats and the diabetic rats treated with ginseng. The mean differences of FFA, FI, glucose and insulin were combined in the random effect model, because of the heterogeneity of the studies. The other factors, TC, TG and glycogen, were combined in the fixed effect model. The levels of FI, glucose and TG of diabetic rats were significantly less than the levels of diabetic rats treated with ginseng. On the other hand, The mean of FFA and TC of diabetic rats were not significantly different with them of diabetic rats with ginseng ($> 0.05$).

To check the publication bias in estimated MDs, the funnel plot and Eggers linear regression test was used. Although the publication biases of combined MD estimates about FFA, FI, glucose, insulin and TC were doubtable, the anti-diabetic effect of ginseng about FI, glucose and insulin were significantly investigated. In conclusion, this study suggests that the anti-diabetic effect of ginseng about level of FI, glucose, insulin, TG and glycogen are significant.

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