The effect of glutathione S-transferase $M1$ and $T1$ polymorphisms on blood pressure, blood glucose, and lipid profiles following the supplementation of kale ($Brassica oleracea acephala$) juice in South Korean subclinical hypertensive patients

Jeong-Hwa Han¹, Hye-Jin Lee¹, Tae-Seok Kim² and Myung-Hee Kang¹

¹Department of Food and Nutrition, College of Life Science and Nano-technology, Hannam University, 461-6 Jeonmin-dong, Yuseong-gu, Daejeon 305-811, Korea
²R&D Center, Pulmuone Co., Ltd., Seodaemun-gu, Seoul 120-600, Korea

BACKGROUND/OBJECTIVES: Glutathione S-transferase (GST) forms a multigene family of phase II detoxification enzymes which are involved in the detoxification of reactive oxygen species. This study examines whether daily supplementation of kale juice can modulate blood pressure (BP), levels of lipid profiles, and blood glucose, and whether this modulation could be affected by the $GSTM1$ and $GSTT1$ polymorphisms.

SUBJECTS/METHODS: 84 subclinical hypertensive patients showing systolic BP over 130 mmHg or diastolic BP over 85 mmHg received 300 ml/day of kale juice for 6 weeks, and blood samples were collected on 0-week and 6-week in order to evaluate plasma lipid profiles (total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol) and blood glucose.

RESULTS: Systolic and diastolic blood pressure was significantly decreased in all patients regardless of their $GSTM1$ or $GSTT1$ polymorphisms after kale juice supplementation. Blood glucose level was decreased only in the $GSTM1$-present genotype, and plasma lipid profiles showed no difference in both the $GSTM1$-null and $GSTM1$-present genotypes. In the case of $GSTT1$, on the other hand, plasma HDL-C was increased and LDL-C was decreased only in the $GSTT1$-present type, while blood glucose was decreased only in the $GSTT1$-null genotype.

CONCLUSIONS: These findings suggest that the supplementation of kale juice affected blood pressure, lipid profiles, and blood glucose in subclinical hypertensive patients depending on their GST genetic polymorphisms, and the improvement of lipid profiles was mainly greater in the $GSTT1$-present genotype and the decrease of blood glucose was greater in the $GSTM1$-present or $GSTT1$-null genotypes.

Keywords: Brassica, GST polymorphism, hypertension, lipid profiles, blood glucose

INTRODUCTION

Glutathione S-transferases (GSTs), a family of phase II enzymes found in all eukaryotic species, play a critical role in detoxifying both naturally occurring and xenobiotic compounds, including carcinogens, environmental toxins, and reactive oxygen species, by catalyzing the transfer and conjugation of glutathione [1]. Eight classes of mammalian cytosolic GSTs are currently recognized, designated as alpha (A), mu (M), kappa (K), omega (O), pi (P), sigma (S), theta (T), and zeta (Z) [2]. Among them, both $GSTM1$ and $GSTT1$ are known to be polymorphic in humans and both of them have null alleles resulting from gene deletion [3]. The null genotypes (homozygous for the non-functional allele) of $GSTM1$ and $GSTT1$ have a decreased capability of detoxifying some carcinogens. Also, GST genetic polymorphisms imply variations in enzyme activities that can result in oxidative stress susceptibility through alterations in GSH metabolism [4]. Because of the role of GSTs in detoxifying xenobiotics and the products of oxidative stress, the effect of GST deletion has been investigated for numerous conditions. Meta-analyses have indicated that the deletion of either $GSTM1$ or $GSTT1$ is associated with a significant increased risk of coronary heart disease [5], and several forms of cancer [6-8]. Several epidemiological studies indicated that cancer and cardiovascular diseases share common risk factors [9].

Cruciferous vegetables are widely consumed in people's diets. These vegetables include kale, as well as broccoli, cauliflower, radish, Brussels sprouts, watercress, and cabbage and are...
consumed either fresh (salads), cooked, or in vegetable juices. Kale, classified into the **Brassica oleracea** species (**Brassica oleracea acephala**), is one of the most popular cruciferous vegetable consumed in South Korea. Besides nutritional components, these vegetables are also rich in health beneficial secondary metabolites, which include sulfur containing glucosinolates, flavonoids, anthocyanins, coumarins, carotenoids, antioxidant enzymes, terpenes, and other minor compounds [10]. Glucosinolates upon hydrolysis form biologically active compounds such as indoles and isothiocyanates (ITC) [11]. ITC are potentially anticarcinogenic phytochemicals formed from the metabolism of glucosinolates and are found in cruciferous vegetables as well as a number of other foods [12]. ITC are both substrates and inducers of glutathione S-transferase (GST) phase II metabolizing enzymes involved in carcinogen detoxification as well as effectors of phase I pathways [13]. A few human intervention trials have evaluated the ability of the GST genotype to modulate the response to cruciferous vegetable intake on biomarkers [13]. It has been suggested that the capacity of a moderate intake of watercress [14] or cruciferous vegetable [15] to induce detoxification is dependent in part on the GSTM1 genotype. In the same manner, GSTM1 genotypes have a significant effect on the metabolism of sulforaphane derived from glucosinolate broccoli, and this difference in metabolism may explain the greater protection that GSTM1-positive persons gain from consuming broccoli [16].

Hypertensive patients who may be genetically impaired in their ability to handle oxidative stress, by virtue of deletion of the GSTM1 gene, are more susceptible to the impact of ROS exposure. Therefore, supplementation with antioxidants might compensate for this genetic susceptibility [2]. Recently, it has been reported that regular meals supplemented with kale juice could exhibit favorable influence on serum lipid profiles and antioxidant systems, and hence contribute to reduce the risks of coronary artery disease in male subjects with hyperlipidemia [17]. However, little is known about the potential effects of kale juice on human health, especially concerning the effect of GST polymorphisms on any health benefits that kale juice may provide. Therefore, the present study was undertaken to examine whether daily supplementation of kale juice modulates the blood pressure (BP), blood glucose, and levels of lipid profiles in subclinical hypertensive subjects, and whether this modulation could be affected by the GSTM1 and GSTT1 polymorphisms.

**SUBJECTS AND METHODS**

**Participants and dietary intake assessment**

This research was carried out for 6 weeks on male borderline isolated subclinical hypertensive patients [systolic BP (SBP) > 130 mmHg or diastolic BP (DBP) > 85 mmHg] who had never been treated for hypertension. Participants included members of the staff of Hannam University, government employees in Daejeon, and volunteers among the participants of a previous study [18]. The study was conducted according to a study protocol that passed the standards of the Institutional Review Board at Hannam University, South Korea (approval code: 2012-04k). Informed written consent including purpose, nature, and potential risks was obtained from all subjects. Information regarding individual characteristics, health status, and lifestyle factors including smoking, alcohol, and exercise were collected by questionnaires. Participants suffering from poor health or who were consuming prescribed medications were excluded from the study. The participants’ weight, height, and waist and hip circumferences were measured using standard protocols. These measurements were then used for calculating body mass index (BMI) and waist-hip ratio (WHR). Body fat was measured by Bio-electrical Impedance Fatness Analyzer (Inbody 520, Biospace, South Korea). Blood pressure was the mean of three measurements in a seated position, using an automatic BP monitor (Watch BP Home, Microlife, Switzerland) on weeks 0, and 6. Dietary information provided by the participants was recorded using 24-hour recall and a food frequency questionnaire. Total nutrient intake was estimated using the CAN Pro 3.0 (Nutrition Information Committee, Korean Nutrition Society), and evaluated using the Korean Dietary Reference Intakes (2010) [19].

**Kale juice supplementation**

Two bottles (total 300 ml) of 100% pure kale juice (Pulmuone, South Korea) were freshly delivered and supplemented every day to the participants for 6 weeks. The participants were instructed to consume the kale juice daily and record their intake on a daily log. A depletion period restricting the consumption of kale products and fruits and vegetables with high antioxidant nutrients was established 2 weeks prior to the supplementation of kale juice. This period was intended to ensure antioxidant vitamin status within similar levels at baseline. Also, they were reminded and advised over the phone individually to refrain from consuming foods which may affect the antioxidant index during the experimental period.

**Blood analysis**

Blood was drawn from the participants at the beginning (0 week) and after 6 weeks of the supplementation of kale juice. Blood samples drawn from the survey participants after a minimum 12 hours overnight fasting were put in a 10 ml heparinated sterile tube (Vacutainer, Becton Dickinson, U.S.A.), and brought to the laboratory. Some of the blood (500 uL) was put in microcentrifuge tubes separately for the analysis of GSTM1 and GSTT1 polymorphisms. The remaining blood was centrifuged at 1,000 rpm for 15 minutes to collect PRP (platelet-rich plasma), and then it was centrifuged again at 3,000 rpm for 30 minutes to collect PDP (platelet-deficient plasma) following the separation of blood plasma. The blood plasma was divided for each analysis item and kept at -80°C in a freezer until use. The blood glucose level was measured immediately after drawing the blood using a testing device (GLUCOTREND, Roche Diagnostics GmbH, Germany).

**Analysis of GSTM1 and GSTT1 genetic polymorphisms**

The GSTM1 and GSTT1 genotypes were determined as previously described without any modification [20,21]. Briefly, the \( \beta \)-globin primer pair (sense: 5'–CAAATTACATGCCATGCTAC CGG-3' and antisense: 5'-GAAGAGCCAAGGACGTG-3'), which had not been deleted, was used as an internal control. The primers for amplifying the GSTM1 gene were (sense) 5’–CGCCATCTTGTGCTACATTGGCCGTC-3'.
and (antisense) 5'-TTCTGGATTGTAGCAGATCA-3'. The primers for the GSTT1 gene were (sense) 5'-TTCTTCTACTGTGCTCATCCTC-3' and (antisense) 5'-TCACCGCATCAGGCAAGCA-3'. The polymerase chain reaction (PCR) was performed in a 50 μL reaction mix containing 0.1 μg DNA, 5 mM deoxyribonucleoside triphosphates, 30 pmol of each primer, 30 mM MgCl2, and 0.5 U thermos table Taq DNA polymerase. After 2 minutes of pretreatment at 95 °C the reaction was subjected to 30 cycles of amplification at 94 °C for 1 minute, annealing at 64 °C for 1 minute, and 1 minute of elongation at 72 °C. A final extension step of 7 min at 72 °C terminated the process. The products of the PCR amplification were separated by electrophoresis in a 1.5% agarose gel and stained with ethidium bromide (0.1 μg/mL). The internal standard fragment was obtained for the β-globin gene. The absence of amplified product was consistent with the null genotypes. All reagents and chemicals for the genetic polymorphism were purchased from Bioneer (South Korea).

**Determination of plasma lipid profiles**

Plasma lipid, total cholesterol, triglyceride, and HDL-Cholesterol contents were analyzed using a semi-auto biochemistry analyzer (Shining Sun A6, Beijing Shining Sun Technology, China) with 1 ml of enzyme solution from a kit reagent produced by STANBIO Laboratory (U.S.A.) and reactivated for 5 minutes in a water bath under 37 °C. LDL-Cholesterol was calculated using the Friedewald equation [22].

\[
\text{LDL-Cholesterol} = \text{Total cholesterol} - \text{HDL-Cholesterol} - (\text{Triglyceride}/5) \ (\text{mg/dl})
\]

**Statistical analysis**

All the data were entered into a Microsoft Excel database and the statistical tasks were performed with the SPSS-PC+ statistics package (version 20.0). Mean and standard error of the mean (S.E) were obtained for each item, and the mean difference among the 4 types of polymorphism of the 2 groups (GSTM1 null and present types; GSTT1 null and present types) was verified by independent t-test, and all statistical significances evaluated at the level of α = 0.05. The significance of the mean comparison before and 6 weeks after supplementations of kale juice was tested by paired t-test. Also, a chi-square test was performed on the frequency of smoking habits, existence of alcohol intake, and exercise habits.

**RESULTS**

**General characteristics of the participants**

General characteristics of the participants are shown in Table 1. All of the participants in this study were aged 20-57 years, and the average age was 38 years. After 6 weeks of kale juice supplementation, the percentage body fat of the participants was decreased significantly, regardless of GSTM1 or GSTT1 genotype. The WHR of the participants was decreased only in GSTM1-null genotype after 6 weeks of supplementation. Participants' smoking habits indicated a daily average of 13.9 ± 1.4 cigarettes with 11.1 ± 2.1 pack years. The drinking habits of the participants showed that the percentage of drinkers was 81.0% among all participants and the total alcohol consumption was 56.8 ± 5.1 mL/day. The portion of participants who regularly exercised was 79.8% and the average exercise time was 30.3 ± 2.9 min/day.

**Nutrient intake of the participants**

Nutrient intake before kale juice supplementation (0 week) and after 6 weeks of supplementation was surveyed using the 24-hour recall method to find out changes in dietary intake

| Variables          | GSTM1 genotype              | GSTT1 genotype              |
|--------------------|-----------------------------|-----------------------------|
|                    | null (n = 49)               | present (n = 35)            | null (n = 45)               | present (n = 39)            |
|                    | 0 week | 6 weeks | 0 week | 6 weeks | 0 week | 6 weeks | 0 week | 6 weeks |
| Age (years)        |        |         |        |         | 38.1 ± 1.5 | 38.4 ± 1.8 | 37.9 ± 1.8 | 38.1 ± 1.5 | 38.4 ± 1.8 | 37.9 ± 1.8 | 38.1 ± 1.5 | 38.4 ± 1.8 |
| Height (cm)        | 171.0 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 | 171.1 ± 0.8 |
| Body weight (kg)   | 73.2 ± 1.5 | 73.0 ± 1.5 | 78.0 ± 1.7 | 77.6 ± 1.7 | 76.1 ± 1.6 | 74.2 ± 1.7 | 73.9 ± 1.7 | 73.9 ± 1.7 | 73.9 ± 1.7 | 73.9 ± 1.7 | 73.9 ± 1.7 | 73.9 ± 1.7 |
| BMI (kg/m²)        | 25.0 ± 0.4 | 24.9 ± 0.4 | 26.0 ± 0.5 | 25.9 ± 0.5 | 25.7 ± 0.5 | 25.6 ± 0.5 | 25.1 ± 0.5 | 25.0 ± 0.5 | 25.0 ± 0.5 | 25.0 ± 0.5 | 25.0 ± 0.5 | 25.0 ± 0.5 |
| Waist-hip ratio (WHR) | 0.881 ± 0.006 | 0.877 ± 0.006* | 0.898 ± 0.006 | 0.894 ± 0.006 | 0.892 ± 0.006 | 0.889 ± 0.006 | 0.883 ± 0.006 | 0.879 ± 0.006 | 0.879 ± 0.006 |
| Body fat (%)       | 23.4 ± 0.9 | 22.7 ± 0.9** | 24.7 ± 1.3 | 23.9 ± 1.3** | 25.1 ± 1.1 | 24.4 ± 1.1** | 22.7 ± 0.9 | 21.9 ± 0.9** |

**Smoking habits**

- Smokers (n (%))
- Cigarettes/day
- Smoking years
- Pack-years

**Drinking habits**

- No. of drinker (n (%))
- Drinks (ml/day)

**Exercise habits**

- Regular exercisers (n (%))
- Exercise time (min/day)

---

1) All values are means ± SE
2) Pack-years: (Cigarettes smoked/day × years smoked)/20
* P < 0.05, ** P < 0.01
The effect of kale juice according to GST polymorphism

During the 6 weeks of kale juice supplementation. The result is shown in Table 2. The nutrient intake showed that the participants maintained their usual intake in energy, protein, fat, carbohydrate, calcium, vitamin C, vitamin E, vitamin A, and retinol before and after kale juice supplementation (Table 2). The nutrient contents of 300 ml of kale juice are: 30 kcal of energy, 4 g of carbohydrate, 4 g of sugars, 4 g of protein, 1253.4 mg of calcium, and 230 mg of total polyphenols.

GSTM1 and GSTT1 polymorphism frequency analysis

Among 84 participants, the GSTM1-null genotype was found in 49 (58.3%) and the GSTM1-present genotype in 35 (41.7%) (Table 3). The GSTT1-null genotype was found in 45 participants (53.6%) and the GSTT1-present genotype in 39 (46.4%). The number of participants who had both the GSTM1 and GSTT1 present genotypes was 13 (15.5%), and those who had either one of the present genotypes was 48 (57.1%), and who had neither of the present genotypes was 23 (27.4%).

Changes in blood pressure

The changes in blood pressure of the participants after kale juice supplementation showed that the systolic and the diastolic pressures were decreased in the participants when divided according to GST polymorphism (Table 4). Systolic pressure was decreased by 5.0% and 3.7% in the GSTT1-null genotype, and also the systolic and diastolic pressures were decreased by 5.2% and 3.1%, respectively, in the GSTM1-present genotype. In the case of GSTT1, on the other hand, the systolic and diastolic pressures were significantly decreased by 4.4% and 3.6% in the GSTT1-null genotype, and 6.0% and 4.2% in the GSTT1-present genotype, respectively, after kale juice supplementation.

Comparison of blood glucose and plasma lipid levels

The results of blood glucose, plasma total cholesterol (TC), LDL-C, HDL-C, and triglyceride (TG), before and after 6 weeks of kale juice supplementation are shown in Fig. 1 and 2. The
blood glucose levels of the participants were significantly decreased in the GSTM1-present and GSTT1-null genotypes (Fig. 1). The plasma TC and TG levels of the participants were not changed after kale juice supplementation regardless of GST polymorphisms. The plasma HDL-C level was significantly increased, and the plasma LDL-C level was significantly decreased after kale juice supplementation in the GSTT1-present genotype, but those levels in the GSTM1-null, GSTM1-present, and GSTT1-null genotypes were not significantly changed after kale juice supplementation (Fig. 2).

**DISCUSSION**

Lack of consistent GSTM1 and GSTT1 modulation of cruciferous vegetable intervention studies is probably due to multiple factors, including tissue-specific responses, differences in end points measured, and the type and amount of crucifers fed [13]. It is unknown whether these differences in glucosinolate profiles, and therefore ITC, lead to different biological effects in humans; however, several laboratories have shown differences in the potency and function of ITC in vitro [23-25]. Navarro et al. [13] reported that individuals with one or more null genotypes of GSTM1 or GSTT1 responded to a greater extent than individuals with both genotypes intact. These results also suggest that the intact GSTT1 allele may be compensating for the lack of active GSTM1 enzyme activity by playing a larger role in ITC metabolism among GSTM1-null individuals; when both alleles are absent, this compensation is no longer possible [13].

The aims of this study were to assess a GSTM1 and/or GSTT1 genotype-dependent effect of kale juice consumption on the blood pressure, glucose, and lipid profiles found in human plasma in subclinical hypertensive patients. In this study, there was a significant reduction of blood pressure after kale juice supplementation in both GSTM1-null and -present as well as GSTT1-null and -present individuals, however, the genetic polymorphisms of GSTM1 and GSTT1 are not associated with SBP and DBP reduction in subclinical hypertensive patients. From these results, it is suggested that this blood pressure reducing effect is more dependent on the composition of kale juice than on GSTM1 or GSTT1 polymorphisms. Furthermore, it is worth noticing that the reduction of blood pressure of GSTT1-present individuals was higher than those of GSTT1-null, as well as those of GSTM1-present or GSTM1-null individuals. Several studies have shown that blood pressure variation between 30% and 40% in a population is thought to have a genetic basis [26]. The results of our previous study of smokers indicated that the reduction of DBP was only observed in GSTM1-null, GSTT1-null, or GSTT1-present individuals after the 8-weeks of grape juice supplementation [27]. However, Saadat et al. [28] showed that alteration in SBP was only observed in subjects who possess the GSTM1-null, GSTT1-present combination genotype. Conversely, Delles et al. [29] did not find an association between GSTM1 gene variants and hypertension. A number of genome-wide linkage analyses concerned with blood pressure have been reported, and most studies have reported linkage with SBP rather than DBP, but there was no obvious explanation for that [30]. The conflicting results for the GST genes and blood pressure could be due not only to publication bias and sample size but also to extreme gene-
environment interactions characterizing the hypertensive phenotypes [31]. Moreover, this discrepancy could be due to differences in the ethnic, genetic, and environmental background of the population studied [32].

A significant reduction of blood glucose was seen in the GSTM1-present and GSTT1-null genotypes after kale juice consumption. Several researchers have shown that consumption of vegetables in the Brassica family may improve insulin resistance and glycemic control in type 2 diabetes. Bahadoran et al. [33] observed that the consumption of 10g of broccoli sprout powder a day resulted in a significant decrease in serum insulin concentration and improved insulin resistance in type 2 diabetic patients. Supplementation of type 2 diabetes with high sulfonaphane content broccoli sprouts resulted in increased plasma total antioxidant capacity and decreased oxidative stress index, serum insulin, and insulin resistance [34]. However, there has been no research which observes the modulation of blood glucose level after consumption of Brassica plants in hypertensive patients linked with GST polymorphisms. Several observational studies reported an association between GSTM1 or GSTT1 polymorphisms and the risk of diabetes mellitus. Amer et al. [32] demonstrated that the GSTT1- and GSTM1-null genotypes, alone or combined, are associated with increased risk of type-2 diabetes mellitus. The GSTM1-null genotype had an effect on glycemic control in type-2 diabetes patients, but they did not observe any significant effect of GSTT1-null on glycemic control. US-based epidemiologic study have correlated broccoli or crucifer consumption with the risk of cancer stratified by GSTM1 genotype, which suggests that GSTM1-present persons gain a greater protection than do GSTM1-null persons [16]. So, it is hypothesized that, due to the potential differences in ITC metabolism between GSTM1-present and GSTM1-null individuals [35], blood glucose differs by GSTM1 genotype. However, in this study’s result, a decrease of blood glucose in the GSTT1-null genotype was also observed in addition to the decrease in the GSTM1-present genotype after kale juice supplementation. Reasons for these modulations are unclear. Further research is needed on the modulation of blood glucose by GSTM1 and/or GSTT1 polymorphisms and on the difference of the mechanism by which kale juice contributes to blood glucose.

In individuals from the general population, triglycerides, HDL-cholesterol, and the triglycerides/HDL ratio were significantly associated with a double-deleted genotype, suggesting that individuals without any copy of both the GSTM1 and GSTT1 genes are at increased risk for cardiovascular disease [36]. Amer et al. [32] attempted to evaluate the association of the GSTM1 (present, null) and GSTT1 (present, null) genotypes with different lipid profiles in diabetic subjects. Patients with the GSTT1-null genotype had higher levels of triglycerides and very low-density lipoprotein cholesterol compared to those with the GSTT1-present genotype. In the same manner, our previous observation study showed that TC and LDL-C levels were significantly higher in non-smokers with the GSTT1-null genotype than those with the GSTT1-present genotype [37]. Thus, it was hypothesized that the plasma lipid profiles of individuals with the GSTT1-null genotype who might be susceptible to coronary diseases responded to a greater extent after kale juice interven-
(Angelica keiskei) has an effect compared to the placebo [42]. Another potential limitation is modest sample sizes, which limited our power to further stratify the data by GST genotype and other possibly confounding factors, although significant changes were detected after supplementation. Thus, this study’s results need to be confirmed by a larger-scaled, controlled study in the future.

In summary, our findings suggest that the supplementation of kale juice affected blood pressure, blood glucose, and lipid profiles in subclinical hypertensive patients depending on their GST genetic polymorphisms, and the decrease of blood glucose was greater in the GSTM1-present and GSTT1-null genotypes, and the improvement of lipid profiles were mainly greater in the GSTT1-present genotype. This finding suggests that kale juice intervention might be effective in plasma lipid profile control in the subgroup of hypertensive patients who are GSTT1-present, although the strength of this study’s findings is limited by the sample size of the study. Much larger studies will be required to accurately measure the modest effects of genes, such as GSTT1, and identify the extent of gene-diet interactions. The relationship between genetic susceptibility biomarkers and the expression of a specific genotype needs to be assessed in vitro, in vivo, or in clinical trials of human volunteers [43]. Further investigation is necessary to establish the mechanism by which kale juice contributes to blood pressure, blood glucose, and lipid profile changes in relation to the GSTM1 and GSTT1 genotypes.

ACKNOWLEDGEMENTS

The authors sincerely appreciate Pulmuone Co., Ltd. for the supply of fresh kale juice for daily supplementation.

REFERENCES

1. Manfredi S, Calvi D, del Fiandra M, Botto N, Biagini A, Andreassi MG. Glutathione S-transferase T1- and M1-null genotypes and coronary artery disease risk in patients with Type 2 diabetes mellitus. Pharmacogenomics 2009;10:29-34.
2. Bessa SS, Ali EM, Hamdy SM. The role of glutathione S-transferase T1 and T1 gene polymorphisms and oxidative stress-related parameters in Egyptian patients with essential hypertension. Eur J Intern Med 2009;20:625-30.
3. Pemble S, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM, Ketterer B, Taylor JB. Human glutathione S-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. Biochem J 1994;300:271-6.
4. Aydemir B, Onaran I, Kiziler AR, Alici B, Akyolcu MC. Increased oxidative damage of sperm and seminal plasma in men with idiopathic infertility is higher in patients with glutathione S-transferase Mu-1 null genotype. Asian J Androl 2007;9:108-15.
5. Wang J, Zhou L, Huang S, Lu F, Lang X, Han L, Song Z, Xu Z. Genetic polymorphisms of glutathione-S-transferase genes GSTM1, GSTT1 and risk of coronary heart disease. Mutagenesis 2010;25:365-9.
6. Qiu LX, Yuan H, Yu KD, Mao C, Chen B, Zhan P, Xue K, Zhang J, Hu XC. Glutathione S-transferase M1 polymorphism and breast cancer susceptibility: a meta-analysis involving 46,281 subjects. Breast Cancer Res Treat 2010;121:703-8.
7. Liao C, Cao Y, Wu L, Huang J, Gao F. An updating meta-analysis of the glutathione S-transferase T1 polymorphisms and colorectal cancer risk: a HuGE review. Int J Colorectal Dis 2010;25:25-37.
8. Wang B, Huang G, Wang D, Li A, Xu Z, Dong R, Zhang D, Zhou W. Null genotypes of GSTM1 and GSTT1 contribute to hepatocellular carcinoma risk: evidence from an updated meta-analysis. J Hepatol 2010;53:508-18.
9. Hansen ES. International Commission for Protection Against Environmental Mutagens and Carcinogens. ICF/EMC Working Paper 7/1/2. Shared risk factors for cancer and atherosclerosis—a review of the epidemiological evidence. Mutat Res 1990;239:163-79.
10. Manchali S, Chidambaram Murthy KN, Patil BS. Crucial facts about health benefits of popular cruciferous vegetables. J Funct Foods 2012;4:94-106.
11. Shapiro TA, Fahey JW, Dinkova-Kostova AT, Holtzclaw WD, Stephenson KK, Wade KL, Ye L, Talalay P. Safety, tolerance, and metabolism of broccoli sprout glucosinolates and isothiocyanates: a clinical phase I study. Nutr Cancer 2006;55:53-62.
12. Steck SE, Gammon MD, Hebert JR, Wall DE, Zeisel SH, GSTM1, GSTT1, GSTP1, and GSTA1 polymorphisms and urinary isothiocyanate metabolites following broccoli consumption in humans. J Nutr 2007;137:904-9.
13. Navarro SL, Chang JL, Peterson S, Chen C, King IB, Schwarz Y, Li SS, Li L, Potter JD, Lampe JW. Modulation of human serum glutathione S-transferase A1/2 concentration by cruciferous vegetables in a controlled feeding study is influenced by GSTM1 and GSTT1 genotypes. Cancer Epidemiol Biomarkers Prev 2009;18:2974-8.
14. Hofmann T, Kuhnert A, Schubert A, Gill C, Rowland IR, Pool-Zobel BL, Glei M. Modulation of detoxification enzymes by watercress: in vitro and in vivo investigations in human peripheral blood cells. Eur J Nutr 2009;48:843-91.
15. Lampe JW, Chen C, Li S, Prunty J, Grate MT, Meehan DE, Barale KV, Dightman DA, Feng Z, Potter JD. Modulation of human glutathione S-transferases by botanically defined vegetable diets. Cancer Epidemiol Biomarkers Prev 2000;9:787-93.
16. Gasper AV, Al-Janobi A, Smith JA, Bacon JR, Fortun P, Atherton C, Taylor MA, Hawkey CJ, Barrett DA, Mithen RF. Glutathione S-transferase M1 polymorphism and metabolism of sulforaphane from standard and high-glucosinolate broccoli. Am J Clin Nutr 2005;82:1283-91.
17. Kim SY, Yoon S, Kwon SM, Park KS, Lee-Kim YC. Kale juice improves coronary artery disease risk factors in hypercholesterolemic men. Biomed Environ Sci 2008;21:91-7.
18. Han JH, Lee HJ, Choi HJ, Yun KE, Kang MH. Association between oxidative stress and blood pressure in Korean subclinical hypertensive patients. Korean J Nutr 2013;46:126-36.
ration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
23. Zhang Y, Talalay P. Mechanism of differential potencies of isothiocyanates as inducers of anticarcinogenic Phase 2 enzymes. Cancer Res 1998;58:4632-9.
24. Ye L, Zhang Y. Total intracellular accumulation levels of dietary isothiocyanates determine their activity in elevation of cellular glutathione and induction of Phase 2 detoxification enzymes. Carcinogenesis 2001;22:1987-92.
25. Jakubikova J, Bao Y, Sedlak J. Isothiocyanates induce cell cycle arrest, apoptosis and mitochondrial potential depolarization in HL-60 and multidrug-resistant cell lines. Anticancer Res 2005;25:3375-86.
26. Lifton RP. Molecular genetics of human blood pressure variation. Science 1996;272:676-80.
27. Cho MR, Han JH, Lee HJ, Park YK, Kang MH. Purple grape juice supplementation in smokers and antioxidant status according to different types of GST polymorphisms. J Clin Biochem Nutr. Forthcoming 2014.
28. Saadat M, Bahaddini A, Mohabatkar H. Polymorphisms of glutathione S-transferase M1 and T1 modulate blood pressure of individuals chronically exposed to natural sour gas containing sulfur compounds. Biochem Biophys Res Commun 2004;316:749-52.
29. Delles C, Padmanabhan S, Lee WK, Miller WH, McBride MW, McClure JD, Brain NJ, Wallace C, Marçano AC, Schmieder RE, Brown MJ, Caulfield MJ, Munroe PB, Farrall M, Webster J, Connell JM, Dominiczak AF. Glutathione S-transferase variants and hypertension. J Hypertens 2008;26:1343-52.
30. Saadat M, Dadbione-Pour A. Influence of polymorphism of glutathione S-transferase M1 on systolic blood pressure of normotensive individuals. Biochem Biophys Res Commun 2005;326:449-54.
31. Polimanti R, Piacentini S, Lazzarin N, Re MA, Manfioletto D, Fuciarelli M. Glutathione S-transferase variants as risk factor for essential hypertension in Italian patients. Mol Cell Biochem 2011;357:227-33.
32. Amer MA, Ghattas MH, Abo-Elmatty DM, Abou-El-Ela SH. Influence of glutathione S-transferase polymorphisms on type-2 diabetes mellitus risk. Genet Mol Res 2011;10:3722-30.
33. Bahadoran Z, Tohidi M, Nazeri P, Mehran M, Azizi F, Mirmiran P. Effect of broccoli sprouts on insulin resistance in type 2 diabetic patients: a randomized double-blind clinical trial. Int J Food Sci Nutr 2012;63:767-71.
34. Bahadoran Z, Mirmiran P, Azizi F. Potential efficacy of broccoli sprouts as a unique supplement for management of type 2 diabetes and its complications. J Med Food 2013;16:375-82.
35. Brauer HA, Libby TE, Mitchell BL, Li L, Chen C, Randolph TW, Yasui YY, Lampe JW, Lampe PD. Cruciferous vegetable supplementation in a controlled diet study alters the serum peptidome in a GSTM1-genotype dependent manner. Nutr J 2011;10:11.
36. Maciel SS, Pereira Ada C, Silva GJ, Rodrigues MV, Mill JG, Krieger JE. Association between glutathione S-transferase polymorphisms and triglycerides and HDL-cholesterol. Atherosclerosis 2009;206:204-8.
37. Jo HR, Lee HJ, Kang MH. Antioxidative status, DNA damage and lipid profiles in Korean young adults by glutathione S-transferase polymorphisms. Korean J Nutr 2011;44:16-28.
38. Seow A, Shi CY, Chung FL, Jiao D, Hankin JH, Lee HP, Coetzee GA, Yu MC. Urinary total isothiocyanate (ITC) in a population-based sample of middle-aged and older Chinese in Singapore: relationship with dietary total ITC and glutathione S-transferase M1/T1/P1 genotypes. Cancer Epidemiol Biomarkers Prev 1998;7:775-81.
39. Fowke JH, Shu XO, Dai Q, Shintani A, Conaway CC, Chung FL, Cai Q, Gao YT, Zheng W. Urinary isothiocyanate excretion, brassica consumption, and gene polymorphisms among women living in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2003;12:1536-9.
40. Dyba M, Wang A, Noone AM, Goerlitz D, Shields P, Zheng YL, Rivlin R, Chung FL. Metabolism of isothiocyanates in individuals with positive and null GSTT1 and M1 genotypes after drinking watercress juice. Clin Nutr 2010;29:813-8.
41. Zhang Y, Kolm RH, Mannervik B, Talalay P. Reversible conjugation of isothiocyanates with glutathione catalyzed by human glutathione transferases. Biochem Biophys Res Commun 1995;206:748-55.
42. Kim JS, Kim HY, Park YK, Kim TS, Kang MH. The effects of green vegetable juice (Angelica keiskei) supplementation on plasma lipids and antioxidant status in smokers. Korean J Nutr 2003;36:933-41.
43. Kang D, Lee KH, Lee KM, Kwon HJ, Hong YC, Cho SH, Strickland PT. Design issues in cross-sectional biomarkers studies: urinary biomarkers of PAH exposure and oxidative stress. Mutat Res 2005;592:138-46.