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Acute Modulatory Effects of Apple Cider Vinegar, Garlic, Ginger, Lemon and Honey Mixture, with and Without Exercise on Postprandial Glycemia in Non-Diabetic Females

(Kesan Modulasi Akut Campuran Cuka Epal, Bawang Putih, Halia, Lemon dan Madu ke atas Glisemia Posprandial dengan atau tanpa Senaman dalam Wanita Tanpa Diabetes)

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ABSTRACT

Postprandial hyperglycemia is independently related to cardiovascular disease. Garlic, ginger, lemon, honey and apple cider vinegar are known to have anti-glycemic properties. However, the effectiveness of combination of these natural products on reducing postprandial glycemia is uncertain. The aim of the present study was to investigate the glucose-lowering effect of a novel mixture consisting of apple cider vinegar, garlic, ginger, lemon, and honey; alone and in combination with exercise in response to a high-carbohydrate meal in non-diabetic individuals. Ten, female subjects (mean age: 25 ± 2.67 years, mean BMI: 22.6 ± 3.5 kg/m²) participated in this randomised, cross-over intervention consisting of four trials: control (CON), mixture only (MIX), exercise only (EX), and exercise + mixture (EX-MIX). All trials involved consumption of a high-carbohydrate breakfast, then followed by rest in CON, consumption of natural product mixture in MIX, brisk-walking exercise in EX, and combination of mixture and exercise in EX-MIX. Blood glucose was measured at fasting, and at 30, 60, 90, 120 minutes post meal. Postprandial glucose response was calculated as area under the glucose curve. Two-way repeated measures ANOVA showed a significant group and time interaction ($p < 0.001$). Compared to CON, postprandial glucose responses were 8%, 13% and 15% lower in MIX ($p = 0.049$), EX ($p = 0.001$) and EX-MIX ($p = 0.005$) respectively. Postprandial glucose was 8% lower in EX-MIX compared to MIX ($p = 0.002$). In conclusion, consuming natural product mixture containing garlic, ginger, lemon, honey and apple cider vinegar reduced postprandial glycemia to a certain extent, however, combining mixture with exercise produced a greater attenuation effect compared to consuming mixture alone. This finding is indicative of a potential benefit of the novel mixture as a complementary management of hyperglycemia in high-risk individuals.

Keywords: Natural products; glucose; hyperglycemia; exercise

ABSTRAK

Hiperglisemia posprandial adalah berkait dengan penyakit kardiovaskular. Bawang putih, halia, lemon, madu dan cuka epal terbukti mempunyai sifat anti-glisemik. Namun, keberkesanan campuran produk asli tersebut dalam mengurangkan glisemia posprandial belum diketahui. Tujuan kajian ini adalah untuk menentukan kesan campuran bawang putih, halia, lemon, madu dan cuka epal terhadap penurunan respons glukosa posprandial, dan dengan gabungan senaman selepas diberi makanan tinggi karbohidrat dalam individu tanpa diabetes. Sepuluh subjek wanita (purata umur: 25 ± 2.67 tahun, purata IJT: 22.6 ± 3.5 kg/m²) telah mengambil bahagian dalam intervensi berbentuk rawak silang yang terdiri daripada empat jenis intervensi: kawalan (CON), campuran produk asli (MIX), senaman sahaja (EX) dan senaman + campuran produk asli (EX-MIX). Kesemua intervensi melibatkan sarapan tinggi karbohidrat, diikuti dengan rehat bagi intervensi CON, minuman campuran produk asli selepas sarapan bagi intervensi MIX, senaman selepas sarapan bagi intervensi EX, dan gabungan minuman produk asli dan senaman bagi intervensi EX-MIX. Aras glukosa darah ditentukan sebelum sarapan (0 minit) dan pada 30, 60, 90 dan 120 minit selepas sarapan. Respons glukosa posprandial diukur menggunakan keluasan di bawah lengkuk glukosa. Analisis ANOVA dua-hala menunjukkan interaksi kumpulan dan masa yang signifikan ($p < 0.001$). Respons glukosa posprandial adalah lebih rendah sebanyak 8%, 13% dan 15% dalam MIX ($p = 0.049$), EX ($p = 0.001$) and EX-MIX ($p = 0.005$) masing-masing berbanding kawalan. Respons glukosa posprandial juga adalah 8% lebih rendah dalam EX-MIX berbanding MIX ($p = 0.002$). Secara kesimpulan, gabungan campuran produk asli mengandungi bawang putih, halia, lemon, madu dan cuka epal dapat menurunkan respons glukosa posprandial, namun gabungan campuran produk asli dengan senaman menghasilkan penurunan glukosa posprandial yang lebih berkesan. Dapatan kajian ini menunjukkan potensi campuran produk asli ini sebagai salah satu kaedah komplementari dalam pengurusan hiperglisemia dalam individu yang berisiko.

Kata kunci: Produk asli; glukosa; hiperglisemia; senaman

INTRODUCTION

Postprandial hyperglycemia is characterized by abnormally increased circulating levels of glucose in the blood following a meal. Accumulating evidence supports the critical role of acute postprandial hyperglycemia to incrementally contribute to cardiovascular risk; it better predicts CVD-related deaths compared with fasting glucose concentrations, regardless of the presence of diabetes (Gerich 2003). Hyperglycemia can cause serious damage to the nerves and blood vessels, leading to macro- and microvascular complications often seen in diabetes. Mechanistic evidence suggests that the adverse effects of hyperglycemia on vascular and nervous functions are mediated through oxidative stress (Ceriello & Genovese 2016), increased formation of advanced glycation end products (AGEs) (Nishikawa & Araki 2016) and more importantly, promotion of inflammatory state (Hansen et al. 2017). Due to the fact that postprandial hyperglycemia is implicated in the altered metabolic flux contributing to accelerated CVD progression, therefore reducing postprandial hyperglycemia is now becoming a main target in the prevention and treatment of metabolic diseases.

The management of hyperglycemia includes pharmacological interventions, physical exercise, and change of lifestyle and diet. The use of natural products as an alternative therapy for management of hyperglycemia has grown exponentially over the past decade. Studies on the potential role of natural products preparation, either as pure compounds or as extracts, as having hypoglycemic effects is rapidly gaining focus. With a good safety profile and convenience, natural product-based supplements have increasingly become attractive additions to the regular pharmacological therapies in the context of prevention or treatment of cardiovascular and metabolic diseases (Waltenberger et al. 2016). Indeed, many natural products are currently being sold in the mass market as food supplements for promoting general health or as herbal remedies. Vinegar, garlic (*Allium sativum*), ginger (*Zingiber officinale*) lemon (*Citrus limon*) and honey have been widely used as dietary spices and natural remedies of various ailments in folk medicine for centuries (Beidokhti et al. 2017; Budak et al. 2014; Samarghandian et al. 2017). Individually, they have been shown to exert hypoglycemic effects by a number of mechanisms: facilitation of insulin-dependent glucose uptake by increasing translocation of glucose transporter GLUT4 to the cell membrane surface (Li et al. 2012), delaying gastric emptying (Hlebowicz et al. 2007), and enhanced hepatic glucose uptake and glycogen synthesis (Erejuwa et al. 2012). Here in Malaysia, the combination of these natural products is among the widely-marketed food supplements for treating diabetes-related symptoms as well as maintenance of general health. While these natural products may have been shown to have anti-hyperglycemic properties individually (Bayan et al. 2014; Erejuwa et al. 2012; Farideh et al. 2017; Sharma et al. 2015; Shidfar et al. 2015), there is little to no evidence to support the ability of these combined agents to effectively lower blood glucose levels. Nevertheless, the usage of these herbal food supplements should not be discounted by healthcare professionals now that they are becoming increasingly popular, especially for those whose blood glucose levels are on the borderline and pharmacological therapies have not been initiated (Deng 2012).

Therefore, the aim of this study was to evaluate the effect of a natural products mixture consumption containing apple cider vinegar, garlic, ginger, lemon and honey on postprandial blood glucose in response to a high-carbohydrate meal. To further evaluate the effectiveness of the mixture, we compared the effect of the mixture against acute exercise, as exercise has been shown to effectively attenuate postprandial hyperglycemia (Farah & Gill 2013). Therefore, this study examined the effects of consumption of natural products mixture, with or without exercise, on postprandial hyperglycemia, in untrained, non-diabetic young women. We postulated that the consumption of the natural product mixture yielded glucose-lowering effect comparable to that of exercise, and combination of the mixture with exercise produced an additive effect in lowering postprandial hyperglycemia compared to consumption of natural product mixture alone.

MATERIALS AND METHODS

PARTICIPANTS

Ten, untrained, apparently healthy females (mean age: 25 ± 2.6 years; mean BMI: 22.6 ± 3.5 kg/m^2) were recruited as subjects for this study. The research protocol was conducted in accordance with the ethical standards involving human research and approved by the UKM Medical Center Ethical Review Board (NN-2017-109). All participants gave written informed consent to serve as study subjects. The exclusion criteria include: 1) use of any tobacco product or nutritional supplements that may affect blood glucose, 2) have a clinical diagnosis of cardiovascular or metabolic diseases, and 3) regular exercise at least two d/week for the past six months, and 4) allergy or intolerance to natural products used in the study. Subjects were instructed not to engage in any physical training, alter their habitual dietary patterns or take any other supplements during the study period.

EXPERIMENTAL DESIGN

The study employed a randomised, cross-over intervention, consisted of four postprandial intervention trials: 1) control (CON); 2) natural product mixture only (MIX); 3) exercise only (EX); and 4) combination of exercise and natural product mixture (EX-MIX). Subjects were required to complete all trials. The wash-out period between each trial was seven days. The order of trials was randomized for each subject to minimise bias.

EXPERIMENTAL TRIALS

Figure 1 showed the general overview of the experimental protocol. All test days started in the morning with a standardised test meal, followed by a 2-hour observation in the postprandial period. The four trials were described below:

Control (CON). Subjects consumed a standardised test meal after reporting to the lab, followed by rest thereafter.

Natural product mixture (MIX). Subjects consumed a standardised test meal along with 20 ml of the natural product mixture, followed by rest thereafter.

Exercise (EX). Following a standardised test meal, subjects performed a brisk walking exercise on a treadmill for 20 minutes, followed by rest thereafter.

Exercise and mixture (EX-MIX). Following a standardised test meal along with 20 ml of the natural products mixture, subjects performed a brisk walking exercise on a treadmill for 20 minutes, and followed by rest thereafter.

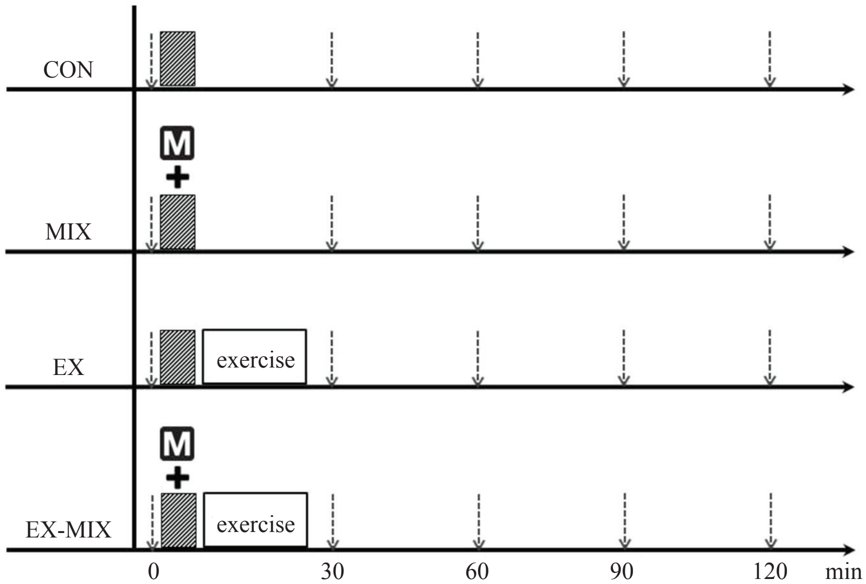

FIGURE 1. Overview of experimental trials for CON: control; MIX: mixture only; EX: exercise only; EX-MIX: exercise + mixture. Consumption of 400-kcal test meal (▧) and natural product mixture (M) are indicated. Blood samples (⇣) were collected at times indicated.

PREPARATION OF NATURAL PRODUCT MIXTURE

A mixture consisting of apple cider vinegar, garlic, ginger, lemon juice and pure 'kelulut' honey was prepared based on a ratio of 1: 1: 1: 1: 1. A feasibility test was conducted to test the palatability of the mixture for subjects' consumption. The formulation mixture contained equal quantities of 40 ml of ginger juice (225 g/milled and refined), garlic juice (100 g/milled and refined), pure lemon juice, apple cider vinegar and honey (modified from Naseem et al. 2016). All liquid except honey were reduced to one-fourth of original volume on medium heat for 30 minutes. The concentrated mixture was then cooled at room temperature before adding honey. The final product mixture was kept chilled in a refrigerator and used within 48 hours.

STANDARDISED TEST MEAL

In all trials, subjects consumed a standardised, high-carbohydrate meal (400 kcal, 83 g carbohydrate) in the morning after an 8-hr overnight fast. The meal consisted of two slices of white bread with 20 g of mixed fruit jam, two pieces of chocolate cookies and 250 ml of sweetened beverage. Timing of meal was kept consistent for all subjects in all trials.

EXERCISE PROTOCOL

Subjects performed a brisk-walking exercise on a motorized treadmill at the intensity of 50-60% of heart rate reserve (HRR), equivalent to a moderate intensity. This was calculated for each individual using the following Karvonen equation: [(220 – age) × % intensity)] + resting heart rate (Swain et al. 1994). Subjects were required to exercise within the individual target heart rates throughout the exercise duration. The speed and inclination were tailored to each subject's preference. Heart rates were recorded every five minutes during the exercise using heart rate monitors (POLAR®, Finland).

BLOOD SAMPLING

Blood samples were collected at fasting (0 min) and at 30, 60, 90 and 120 minutes post test meal in all trials for the determination of plasma glucose using a glucose analyzer (ACCU-CHEK Active, Roche). The total area under glucose versus time curve (AUC 0-120 min), calculated using the trapezium rule, was used as a summary measure of the postprandial glucose response in each trial.

STATISTICAL ANALYSIS

Sample size calculation was primarily based on the number of participants needed to detect a difference in area under the curve (AUC) of postprandial glucose of approximately 20% (Mettler et al. 2009). A priori power calculation indicated that 10 participants would enable detection of a change in postprandial glucose response with 80% power. Data were analyzed using the SPSS (version 22, SPSS Inc.) One-way repeated measures ANOVA was used to compare fasting glucose and area under curve values for postprandial glucose responses across the four trials. Two-way repeated-measures ANOVA (trial × time) were used to compare postprandial glucose changes over time and across the trials, followed by Bonferonni correction for pair-wise comparisons to determine the mean differences between and within trials. Percentages are used to quantify the differences in total AUC (0-120 min) between trials. Data are presented as mean values and their standard errors, unless otherwise stated. Statistical significance was accepted at $p < 0.05$.

RESULTS

RESPONSES DURING EXERCISE

The treadmill speed and gradient for both exercise sessions (EX and EX-MIX) were identical within each subject. Subjects walked for 20 min at an average speed of 5.5 ± 0.1 km/h on a gradient of 2.2 ± 0.8%. All exercise sessions were completed without difficulty and subjects rated the exercise as 'fairly light' on the Borg scale of 6-20 in both the EX and EX-MIX trials. Mean exercise heart rates for the EX and EX-MIX trials were 133 ± 4 bpm and 134 ± 5 bpm respectively. These values did not differ significantly between both trials.

POSTPRANDIAL GLUCOSE RESPONSES

Table 1 and Figure 2 showed the fasting and postprandial glucose responses in all trials. No significant differences were observed in fasting glucose values across the four trials. Two-way repeated measures ANOVA revealed a significant group x time interaction: $F(12, 108) = 6.63$, $p < 0.001$. Plasma glucose peaked at 30 min following the standardized test meal and was lower in the MIX (-10%, $p > 0.05$), EX (-26%, $p = 0.002$) and EX-MIX (-31%, $p = 0.001$) trials compared to CON. Plasma glucose remained significantly lower in the following 60 min in MIX ($p = 0.004$), EX ($p = 0.012$) and EX-MIX ($p = 0.006$) trials compared to CON. There were no differences in plasma glucose across all trials following 120 min.

Analysis showed a significant effect of trials on postprandial glucose AUC_{0-120} across all conditions [$F(4, 12) = 9.89$, $p < 0.001$]. Among all trials, the postprandial glucose AUC was highest in the CON trial. Compared to CON, the postprandial glucose AUC values were 13% and 15% lower in the EX ($p = 0.005$) and EX-MIX ($p = 0.001$) respectively. The postprandial glucose AUC in MIX trial showed an 8% attenuation compared to CON, however this was borderline significant ($p = 0.049$). The postprandial glucose AUC was significantly lower in EX-MIX (-8%, $p = 0.002$) compared to MIX trial. No significant differences were observed in postprandial glucose AUC between EX and MIX and between EX and EX-MIX trials.

DISCUSSION

The aims of this study were to determine the effect of natural product mixture consumption on postprandial glycemia in response to a high-carbohydrate meal, as well as to determine whether the consumption of natural product mixture in combination with exercise produced an additive effect compared to consumption of mixture or exercise alone. To the best of our knowledge, this is the first study employing a novel mixture of apple cider vinegar, garlic, ginger, lemon and honey, and in combination with

TABLE 1. Postprandial glucose responses (mmol/l) and total area under curve (AUC_{0-120} min) across all trials

Trials	0 min	30 min	60 min	90 min	120 min	AUC_{0-120}
CON	4.42 ± 0.35	8.10 ± 2.36	7.21 ± 1.00	6.21 ± 0.93	5.38 ± 0.76	792 ± 115
MIX	4.48 ± 0.32	7.30 ± 0.75[b]	6.13 ± 1.37[a]	6.42 ± 0.80	5.25 ± 0.47	730 ± 86[b]
EX	4.58 ± 0.38	5.94 ± 1.34[a]	5.75 ± 0.84[a]	6.14 ± 0.78	5.50 ± 0.61	684 ± 88[a]
EX-MIX	4.54 ± 0.20	5.56 ± 0.97[a]	6.01 ± 0.95[a]	5.86 ± 0.50[a]	5.27 ± 0.77	670 ± 75[a]

Values are expressed as mean ± SEM, n = 10
CON: control; MIX: mixture only; EX: exercise only; EX-MIX: exercise + mixture
[a] significantly different compared to CON
[b] significantly different compared to EX-MIX

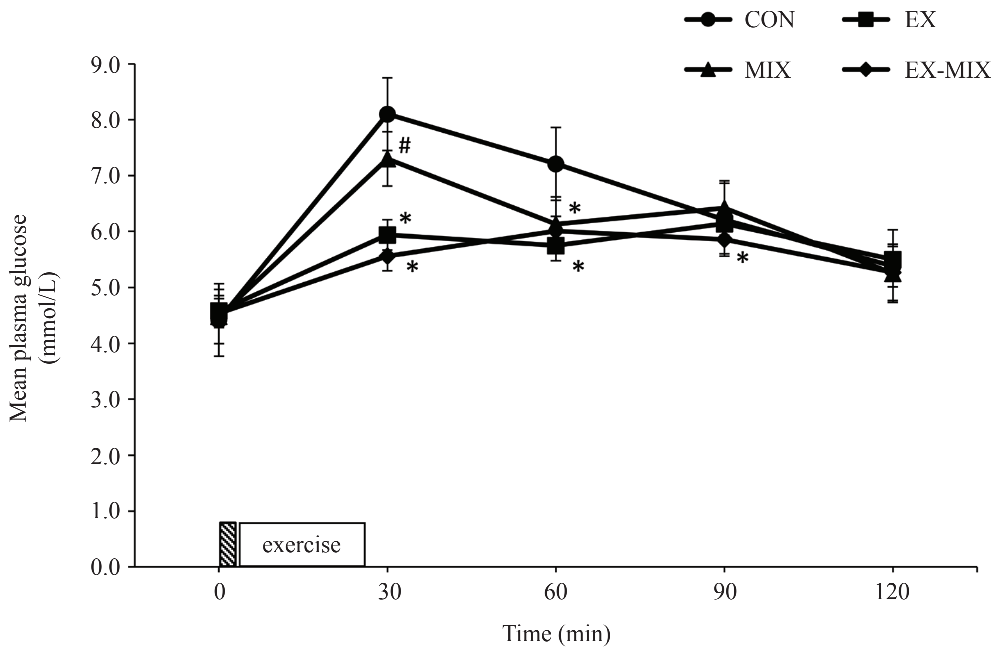

FIGURE 2. Postprandial glucose responses across time 0 to 120 min following standardised test meal (▧) for all trials. Values are means, with SEM represented by vertical bars. CON: control; MIX: mixture only; EX: exercise only; EX-MIX: exercise + mixture. Exercise in EX and EX-MIX trials is indicated on the timeline. * significantly different compared to CON, # significantly different compared to EX-MIX.

a single bout of exercise in examining its acute effects on postprandial glycemia in humans.

The present data demonstrated that the consumption of the natural product mixture resulted in a trend of reduction in postprandial glycemia by an average of 13% compared to control. Apple cider vinegar, garlic, ginger, lemon and honey are among the functional foods commonly used all around the world, particularly in the Asian countries. So far, the anti-glycemic effects of these products have been investigated in isolation particularly in animal studies. However, the effect of these products when combined is relatively unknown, especially in humans. Previously, Naseem et al. (2016) had demonstrated that administration of a similar mixture (*i.e.* combination of apple cider vinegar, garlic, ginger, honey and lemon) in rabbits fed with atherogenic diet for 15 days attenuated fasting blood glucose levels by 34% compared to the control group. In our study, consumption of the mixture caused a pronounced reduction in postprandial glucose concentration at 60 min post meal, compared to control, in addition to an overall reduction on postprandial glycemia though the difference was not apparent. Nevertheless, the finding can be considered novel and seems to be indicative of the anti-glycemic potential of the products combined together. It is possible that the attenuation would appear significant in hyperglycemic individuals in contrast to normoglycemic or non-diabetic individuals, due to higher glucose peaks and exaggerated postprandial responses in the former population.

While there is no clear mechanism on how the combination of these natural products can lower glycemic response, it is plausible that the anti-glycemic effect was mediated by the synergistic effect of individual products in the mixture, which is consistent with the known benefits of individual products. The hypoglycemic potency of garlic has been attributed to allicin-derived organosulphur compounds, which protect insulin from –SH inactivation by reacting with endogenous thiol-containing molecules such as cysteine, glutathione and serum albumin (Eidi et al. 2006). Compelling data show that ginger extract has hypoglycemic, insulinotropic, and sensitiser effects on diabetic humans (Shidfar et al. 2015) and on experimental animals (Ojewole et al. 2006). Meanwhile, the anti-glycemic effect of acetic acid, the active ingredient in vinegar, has been attributed to delay gastric emptying (Liljeberg & Bjorck 1998) as well as to modulate glycolysis/gluconeogenic cycle in skeletal muscles (Fushimi et al. 2001). Fructose, one the major form of monosaccharide sugar found in honey, was suggested to contribute to the anti-glycemic effects of the honey by delaying gastric emptying and increases hepatic uptake of glucose resulting in decreasing blood glucose concentrations (Erejuwa et al. 2012). The anti-glycemic effect of the mixture in the present study was consistent with the aforementioned reports, which may explain the combined beneficial effects of apple cider vinegar, garlic, ginger, lemon and honey on postprandial glucose response.

The hypoglycemic effects of exercise have been widely documented. Most studies have shown that moderate intensity exercise between 30 to 60 min was effective at lowering postprandial glucose responses post-meal in healthy subjects (Hashimoto et al. 2013;

Roberts et al. 2013; Farah & Gill 2013) as well as in diabetic individuals (Kearney et al. 2016). Consistent with published literature, our findings showed that brisk-walking exercise lowered postprandial glycemia by 15% following a high-carbohydrate meal compared to no-exercise control. Exercise is effective in lowering plasma glucose concentration by increasing uptake of glucose into cells by up to 50-fold through the simultaneous stimulation of three key steps: delivery, transport across the muscle membrane and intracellular flux through metabolic processes of glycolysis and glucose oxidation (Sylow et al. 2017). It is noteworthy that the lowering effect of exercise on postprandial glycemia was evident despite the shorter exercise duration (20 min) employed in this study, compared to prolonged duration in previous studies. This finding is somewhat encouraging in the sense that brisk-walking is feasible for most people, which could be generalised into everyday life of hyperglycemic individuals with little motivation for exercise.

When comparing the reduction in postprandial glycemia following consumption of mixture alone, the reduction in glycemic response induced by brisk-walking exercise alone was slightly greater, i.e. 15% vs. 8% in the former, though this finding was not significant. Quite interestingly, this may be indicative of the potential of the natural product mixture to exert an anti-glycemic effect that is comparable to the effect induced by exercise alone. One might speculate that with larger doses than 20 ml used in the study, or with repeated consumption, the lowering effects would be more pronounced. We used a 20 ml dose of mixture, which was approximately equivalent to two tablespoons, a volume that many would typically consume under real-life circumstances with regards to commercially-available natural product supplements. Further investigation may bring more insight regarding the effective dose mixture in lowering postprandial hyperglycemia that is comparable to exercise. Lastly, the study also showed that consumption of the mixture in combination with a short bout of brisk-walking exercise produced greater attenuation in postprandial glycemia compared to mixture alone. This finding was somewhat expected. On the other hand, combining consumption of mixture with exercise did not produce an additive effect in lowering postprandial glycemia compared to exercise alone. The absence of an additive effect could presumably be due to the acute consumption of the natural product mixture. Karimi et al. (2015) in their study in obese women, demonstrated that the combination of water-based exercise and ginger supplement for six weeks had better effect on insulin resistance in comparison to water-based exercise or ginger supplement alone. It is therefore possible, that with prolonged consumption, the additive effect of the natural product mixture and exercise would be more evident.

The findings of the present study might be interpreted in the light of the fact that this was the first study of its kind in human subjects, which could limit our ability to determine the appropriate dose and ratio of the natural product mixture. We believe the dose and ratio of the natural products are vital in determining the anti-glycemic properties of the mixture. Certainly, the conclusion about the modulatory effect of the natural product mixture is only limited to glycemic responses in healthy individuals. Therefore, similar studies examining the effects of different doses and treatment protocol of the mixture on a wider range of variables (e.g. insulin, insulin resistance, blood lipids) would shed more light on the potential benefits of this mixture. No unfavorable effects were observed with the consumption of the natural product mixture in the study.

CONCLUSION

The combination of apple cider vinegar, garlic, ginger, lemon and honey appears to have an anti-hyperglycemic effect on postprandial glycemia in non-diabetic females. In addition, combination of brisk-walking exercise and the mixture produced a greater lowering effect, rather than consuming the mixture alone. The findings of this study may represent a practical, non-pharmacological option in the prevention and management of hyperglycemia in individuals at risk. Future studies with clinically-defined participants, standardised preparation and dose, and across a wide range of metabolic parameters are warranted.

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