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Bioactive Components from Ginger, Tea and Apple Prevent Protein Glycation by Trapping Methylglyoxal with Potential in Alleviation of Diabetic Complications

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Diabetes is the fifth-deadliest disease in the United States. Most diabetes patients die from diabetic complications, such as renal failure, heart attack or stroke. However, diabetic complications are still neither preventable nor curable. New strategies that can prevent, treat, or cure diabetic complications are needed. Increasing evidence has identified the formation of advanced glycation end products (AGEs) as a major pathogenic link between hyperglycemia and diabetes-related complications. In diabetes, formation of AGEs occurs at a higher rate when compared to non-diabetic normal individuals. Alpha-oxoaldehydes such as methylglyoxal (MGO) and glyoxal (GO), the reactive dicarbonyl intermediates generated during the non-enzymatic glycation between reducing sugars and amino groups of proteins, lipids, and DNA, are precursors of AGEs and exert direct toxicity to cells and tissues. Levels of MGO and GO were observed to be 2–6 times higher in diabetic patients' plasma as compared with healthy people's plasma. In addition, this is complicated by many food products and beverages representing exogenous sources of MGO and GO. It is likely that decreasing the levels of MGO and GO and inhibiting the formation of AGEs will form an important component of future therapy in patients with diabetes. Numerous studies have reported that bioactive components in ginger, tea and apple can prevent diabetes and its related complications. However, the underlying molecular mechanisms are still largely unknown. In this project, we investigated the effect of bioactive compounds in ginger ([6]-shogaol (6S) and [6]-gingerol (6G)), tea (epigallocatechin gallate (EGCG)) and apple (phloretin and phloridzin) to inhibit the formation of AGEs via trapping MGO. We demonstrated for the first time that both [6]-shogaol (6S) and [6]-gingerol (6G), the major active components in ginger, markedly trapped MGO in vitro and consequently formed mono-MGO adducts, 6S-MGO and 6G-MGO, which were purified from the respective chemical reaction and characterized as novel compounds by NMR experiments and LC-MS/MS approaches. We

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revealed that the α-carbon of carbonyl group in the side chain of 6S or 6G is the major active site for trapping MGO. We also demonstrated that 6S and 6G could effectively inhibit the formation of MGO-induced AGEs via trapping MGO in a time-dependent manner in the human serum albumin (HSA)-MGO system. Mono-MGO adducts, 6S-MGO and 6G-MGO, were determined to be the major conjugates in 6S- and 6G-treated HSA-MGO assays, respectively, using LC-ESI/MS techniques. These findings showed the potential effects of 6S and 6G on the prevention of protein glycation, suggesting regular consumption of ginger root extract may attenuate the progression of MGO-associated diabetic complications in patients. Similarly, we found that both EGCG and phloretin could inhibit the formation of AGEs through the same pathways. In addition, we also studied whether these compounds could inhibit the formation of AGEs via trapping MGO in high fat diet treated mice. Two different doses of 6G, EGCG and phloretin (25 mg/kg and 75 mg/kg) were given to mice through oral gavage for 16 weeks. Plasma and tissue samples were collected from control and treated mice. The formation of MGO adducts of each compound were analyzed using our established LC/MS methods. The levels of MGO and AGEs were also quantified.