A Composition of Phytonutrients for Glycemic and Weight Management

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Abstract

Maintaining healthy body weight is an important component of any effective diabetes management plan. However, glycemic management using insulin generally leads to weight gain. In addition, weight loss medications prescribed for diabetes management are often associated with adverse side effects, which limit their long-term usage. Alternatively, nutrition intervention provides a safe, readily accessible, and inexpensive option for diabetes management. This study describes a composition of phytonutrients comprising berberine, cinnamaldehyde, and curcumin for glycemic and weight management. Functional complementarity between berberine, cinnamaldehyde, and curcumin provides an effective means to improve insulin sensitivity without increasing adiposity. In primary human omental preadipocytes, cinnamaldehyde and curcumin additively enhance insulin-stimulated activation of Akt2 and glucose uptake, whereas berberine inhibits de novo fatty acid biosynthesis and fat cell differentiation. In a diet-induced obesity murine model, a dietary supplement with berberine, cinnamaldehyde, and curcumin prevents weight gain, improves glucose tolerance, and reduces HbA1c, blood lipids, visceral adiposity, and liver steatosis. Collectively, the composition of phytonutrients comprising berberine, cinnamaldehyde, and curcumin protects against obesity and pre-diabetic conditions in a diet-induced obesity murine model. Safety and efficacy assessment of nutrition intervention using combined berberine, cinnamaldehyde, and curcumin for glycemic and weight management in future clinical trials are warranted.

Results

Cinnamaldehyde and Curcumin Induce Changes to Akt2 Post-translational Modifications

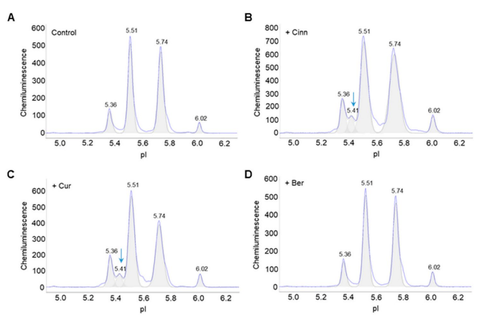

Figure 1. Cinnamaldehyde and curcumin induce changes to Akt2 post-translational modifications. Distribution of Akt2 as a function of isoelectric points in (A) control untreated preadipocytes, or (B–D) preadipocytes treated with (B) cinnamaldehyde, (C) curcumin, or (D) berberine. Arrows point to the appearance of new peaks following treatment versus untreated control.

Cinnamaldehyde and Curcumin Enhance Insulin-stimulated Activation of Akt2

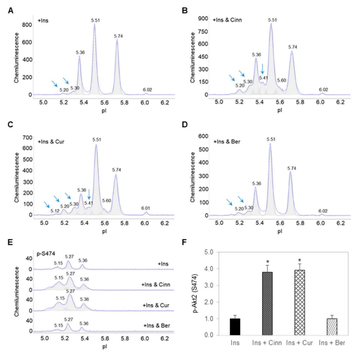

Figure 2. Cinnamaldehyde and curcumin enhance insulin-stimulated activation of Akt2. (A–D) Distribution of Akt2 as a function of isoelectric points in preadipocytes treated with (A) insulin alone, (B) insulin and cinnamaldehyde, (C) insulin and curcumin, or (D) insulin and berberine. (E) Distribution of p-Akt2 (S474) as a function of isoelectric points in preadipocytes treated with insulin alone (top electropherogram), insulin and cinnamaldehyde (second electropherogram), insulin and curcumin (third electropherogram), or insulin and berberine (bottom electropherogram). (F) Relative abundance of p-Akt2 (S474) as a function of treatment condition. Error bars are standard deviations across nine repeated measurements. Asterisk indicates p-value ≤ 0.01 versus treatment with insulin alone.

Additive Effects of Cinnamaldehyde and Curcumin on Akt2 Activation and Glucose Transport

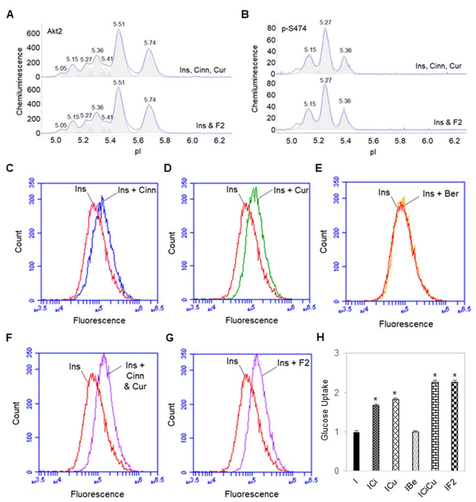

Figure 3. Additive effects of cinnamaldehyde and curcumin on Akt2 activation and glucose transport. (A,B) Distribution of Akt2 (A) and p-Akt2 (S474) (B) as a function of isoelectric points in preadipocytes treated with insulin (Ins), cinnamaldehyde (Cinn), and curcumin (Cur) (top electropherogram) or insulin, cinnamaldehyde, curcumin, and berberine (Ber) (bottom electropherogram). (C–G) 2-NBDG fluorescence in preadipocytes treated with insulin alone (red line) versus treated with (C) insulin and cinnamaldehyde (blue line), (D) insulin and curcumin (green line), (E) insulin and berberine (orange line), (F) insulin, cinnamaldehyde, and curcumin (purple line), or (G) insulin and F2 (cinnamaldehyde, curcumin, and berberine) (purple line). (H) relative abundance of 2-NBDG fluorescence in preadipocytes as a function of treatment condition. I, insulin; ICi, insulin and cinnamaldehyde; ICu, insulin and curcumin; IBe, insulin and berberine; ICiCu, insulin, cinnamaldehyde, and curcumin; IF2, insulin, cinnamaldehyde, curcumin, and berberine.

Berberine Inhibits Fat Cell Differentiation

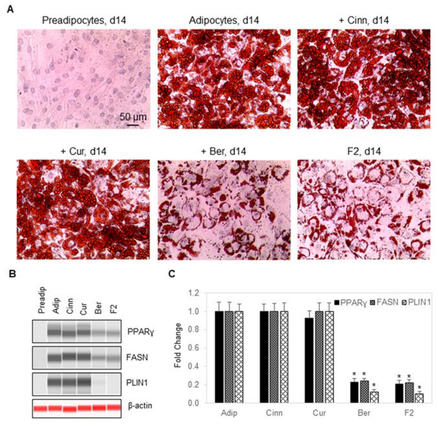

Figure 4. Berberine inhibits fat cell differentiation. (A) Hematoxylin, eosin, and Oil Red O staining of undifferentiated preadipocytes (first panel, upper row), differentiated adipocytes (second panel, upper row), differentiated adipocytes treated with cinnamaldehyde (third panel, upper row), differentiated adipocytes treated with curcumin (first panel, lower row), differentiated adipocytes treated with berberine (second panel, lower row), and differentiated adipocytes treated with an F2 composition comprising cinnamaldehyde, curcumin, and berberine (third panel, lower row). Hematoxylin, eosin, and Oil Red O staining was performed on day 14 post-differentiation. (B) Capillary Western immunoassays to evaluate the expression of adipogenic biomarkers PPARɣ (first row), FASN (second row), and PLIN1 (third row) in undifferentiated preadipocytes (first column), differentiating adipocytes (second column), differentiating adipocytes treated with cinnamaldehyde (third column), differentiating adipocytes treated with curcumin (fourth column), differentiating adipocytes treated with berberine (fifth column), and differentiating adipocytes treated with an F2 composition comprising berberine, cinnamaldehyde, and curcumin (sixth column).

F2 Composition Reduces Weight Gain in Diet-induced Obesity Mice

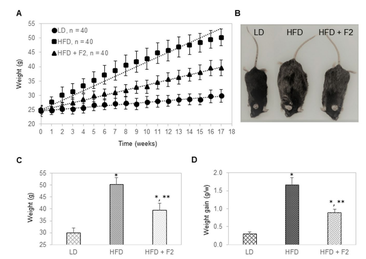

Figure 5. F2 composition reduces weight gain in diet-induced obesity mice. (A) Average body weight as a function of time on specified diets of three groups of mice: Lean diet, high-fat diet, and high-fat diet supplemented with F2. (B) A representative photo of mice from each diet group in week 17. (C) Average body weight in week 17 as a function of mice group on specified diets. LD: Lean diet; HFD: High-fat diet; HFD + F2: High-fat diet supplemented with F2. (D) Average rate of weight gain in grams per week (g/w) as a function of mice group on specified diets. The error bars indicate the standard deviations of 40 mice per animal group.

F2 Composition Improves Glucose Tolerance and Reduces HbA1c in Diet-induced Obesity Mice

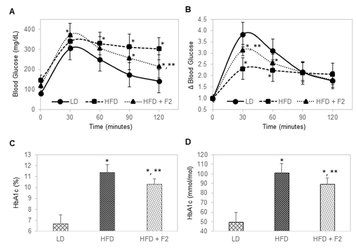

Figure 6. F2 composition improves glucose tolerance and reduces HbA1c in diet-induced obesity mice. (A) Blood glucose level as a function of time post-injection. (B) Fold change in blood glucose level as a function of time post-injection. (C) HbA1c (%) and (D) HbA1c (mmol/mol) as a function of animal groups. LD: Lean diet; HFD: High-fat diet; HFD + F2: High-fat diet supplemented with F2. The error bars indicate the standard deviations of 40 mice per animal group. Single asterisk (*) indicates a statistical significance of p-value ≤ 0.01 versus the lean diet group. Double asterisk (**) indicates a statistical significance of p-value ≤ 0.01 versus the high-fat diet group.

F2 Composition Reduces Blood Lipids in Diet-induced Obesity Mice

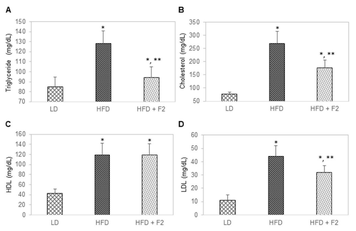

Figure 7. F2 composition reduces blood lipids in diet-induced obesity mice. (A) Triglyceride, (B) cholesterol, (C) high-density lipoprotein (HDL), and (D) low-density lipoprotein (LDL) as a function of animal group on specified diets. LD: Lean diet; HFD: High-fat diet; HFD + F2: High-fat diet supplemented with F2. Blood samples terminally collected after 17 weeks on specified diets were used for measurement. The error bars indicate the standard deviations of 40 mice per animal group. Single asterisk (*) indicates a statistical significance of p-value ≤ 0.01 versus the lean diet group. Double asterisk (**) indicates a statistical significance of p-value ≤ 0.01 versus the high-fat diet group.

F2 Composition Reduces Visceral Adiposity and Liver Steatosis in Diet-induced Obesity Mice

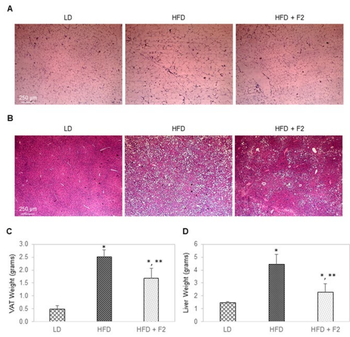

Figure 8. F2 composition reduces visceral adiposity and liver steatosis in diet-induced obesity mice. H&E histology of (A) visceral adipose tissues and (B) liver tissues collected from three animal groups on specified diets. (C) Visceral adipose tissue weight and (D) liver tissue weight as a function of animal groups on specified diets. LD: Lean diet; HFD: High-fat diet; HFD + F2: High-fat diet supplemented with F2. Visceral adipose tissues and liver tissues were terminally collected after 17 weeks on specified diets. The error bars indicate the standard deviations of 40 mice per animal group. Single asterisk (*) indicates a statistical significance of p-value ≤ 0.01 versus the lean diet group. Double asterisk (**) indicates a statistical significance of p-value ≤ 0.01 versus the high-fat diet group.

Conclusions

A composition of phytonutrients comprising berberine, cinnamaldehyde, and curcumin was effective in improving insulin sensitivity without increasing adiposity in a diet-induced obesity murine model. Future clinical assessment is necessary to evaluate safety and efficacy of the composition of phytonutrients comprising berberine, cinnamaldehyde, and curcumin for glycemic and weight management.

References

1. Urasaki Y & Le TT. A composition of phytonutrients for glycemic and weight management. *Nutrients* 14, 3784 (2022). PMID: 36145160.
2. Le TT & Urasaki Y. Composition of phytonutrients for diabetes management. Patent Application No. US 2022/0362227 A1.