

## A Comprehensive review of raisins and raisin components and their relationship to human health\*

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### ABSTRACT

**Purpose:** This literature review was performed to assess the effect of raisins on human health. **Methods:** A review of Medline was conducted using the keywords: ‘raisins, raisins and health, raisins and cardiovascular disease (CVD), raisins and cancer, raisins and diabetes, raisins and fiber, raisins and colon health, raisins and antioxidants, raisins and inflammation, raisins and dental caries’. The reference lists from previous review articles on raisins and human health and the California Raisin Marketing Board files were reviewed for additional studies. **Results:** Raisins have one of the highest polyphenolic content and antioxidant ORAC levels compared to other traditional dried fruits. Many of the polyphenols in raisins are well assimilated and bioavailable. Raisin consumption reduces low density lipoprotein (LDL) cholesterol, blood pressure and blood sugar, when compared to equal caloric carbohydrate snacks and is associated with a reduced risk of CVD. The anti-inflammatory and cancer chemopreventive effects of raisins are mixed. Raisin consumption reduces intestinal transit time and positively affects gut microbiota. Raisins produce sustained energy during long term athletic competitions equal to traditional sports energy gels, shots and jelly beans. Raisins produce a non-cariogenic oral environment and do not fit the American Academy of Pediatrics criteria to be considered a choking hazard. **Conclusions:** Based on the review of literature, consumption of raisins provide numerous health benefits for promoting general wellness and in the prevention of many chronic diseases including: CVD, type 2 diabetes mellitus (T2DM) gastrointestinal diseases, and dental caries.

**KEY WORDS:** raisins, health, diabetes, cardiovascular disease, antioxidants

### Introduction

Raisins (dried grapes), fall into the traditional dried fruit category as they typically contain no added sugar.<sup>1</sup> Raisins constituted the largest global production of a single dried fruit category at 1,234,000 metric tons (MT) in 2015/2016; 296,000 metric tons were produced by the United States, constituting 25% of global production, Turkey produced 196,000 MT, and China and Iran each produced 165,000 MT.<sup>2</sup> Raisin production is expected to be 1.25 million MT in the 2016/17 season. In 2015 raisin supply also had the highest global value of the traditional dried fruits (dates, prunes, dried figs, and dried apricots) at 2,776 million United States Dollars. Worldwide consumption of raisins in 2016/2017 is expected to be 1.23 million tons.<sup>3</sup>

Several recent papers have reviewed various nutritional

and metabolic aspects of raisins. A 2013 review article by Anderson et al.<sup>4</sup> found that raisins reduce glycemia, insulinemia and CVD risk factors. The synergistic effect of raisins and nuts on human health has also been studied. Carughi et al.<sup>5</sup> found numerous health benefits when consuming both raisins and nuts together. Restani’s<sup>6</sup> 2016 review found support for “the suitability of raisins as a source of healthy compounds for human diet”.

In 2011, Bell reviewed the effects of dietary fiber, specifically the fiber found in raisins, on CVD risk, T2DM, cancer, non-cancer bowel disease, and general bowel health. Bell noted that raisins “consumed as a part of a nutrient-dense healthy diet, helped reduce CVD risk”.<sup>7</sup> Kundu et al. conducted a review of the cancer chemoprevention effects of dried fruits and found the antioxidant and anti-inflammatory effects of raisins promising.<sup>8</sup> This paper provides a comprehensive review of

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raisins and human health.

## Methods

A literature review was conducted in Medline using the following descriptors: raisins, raisins and health, raisins and CVD, raisins and cancer, raisins and diabetes, raisins and fiber, raisins and colon health, raisins and antioxidants, raisins and inflammation, raisins and dental caries. The archives of the California Raisin Marketing Board were also reviewed. References in previously published raisin review articles were also reviewed for research on raisins.

## Results & Discussion

### Antioxidants in raisins

#### Content in whole raisins

Raisins are source of polyphenols in the diet, compounds that act as antioxidants in the body.<sup>9,10</sup> The polyphenolic compounds in raisins were assessed by Karadeniz<sup>11</sup> in 2000. Raisin samples (n = 20) included sun-dried (n = 10), dipped (n = 5), and golden (n = 5). Polyphenolics were separated by high-performance liquid chromatography (HPLC), and characterized by their UVvis spectra, and their concentrations measured. Procyanidins and flavan-3-ols were completely degraded in all raisin samples while flavonols remained intact. Raisins were found to be a good dietary source of flavonol glycosides and phenolic acids. Hydroxycinnamates (caftaric and coutaric acids) in sun-dried, dipped, and golden raisins were partially oxidized but were highest in golden raisins treated with sulfur dioxide. Resveratrol was not detected in either grapes or raisins. Yilmaz et al.<sup>12</sup> reported the total phenolic contents

and antioxidant activities of pulp, seed and skin of 22 grape varieties. The antioxidant activity was highest in seeds followed by skins and pulp. Breksa<sup>13</sup> assayed total phenolic compounds for 16 grape varieties and found that trans-Caftaric acid was the predominant compound in all samples.

#### Comparison with other fruits

Raisins compare favorably to other fruits in antioxidant capacity. ORAC values for 12 common fruits in descending order are: 10450, 4302, 3406, 3049, 2103, 1922, 1837, 1640, 1346, 795, 385, and 142, units per 100 g (taken from the United States Department of Agriculture (USDA) database) for golden raisins, strawberries, seedless raisins, apples with skin, oranges, peaches, red grapes, grapefruit, lemons, bananas, pineapples, and watermelon respectively.<sup>14</sup> Fig. 1 shows the total phenolic content of several fruits.<sup>15</sup> Chang et al.<sup>16</sup> reviewed the phytochemical compositions, antioxidant efficacies, and potential health benefits of nine dried fruits. Of these, raisins contained the highest total phenolic count (2,414 mg AAE/100 g), followed by dried apricots, cranberries, peaches, figs, pears, and prunes. Raisins and dates had the highest and lowest ORAC values respectively, (10,450  $\mu\text{mol TE}/100\text{ g}$  and 2,387  $\mu\text{mol TE}/100\text{ g}$ ). Jeszka-Skowron et al.<sup>17</sup> compared antioxidant properties of goji berries, cranberries, and raisins. Goji berries had the highest antioxidant properties of the three, being at least 4-fold higher than the extracts obtained from dried cranberries or raisins. The antioxidant activity of cranberries and raisins was not significantly different.

#### Activity of antioxidants

Kaliora et al.<sup>18</sup> found that extracts of sultanas and currants exhibited 1,1-diphenyl-2-picrylhydrazyl scavenging activity

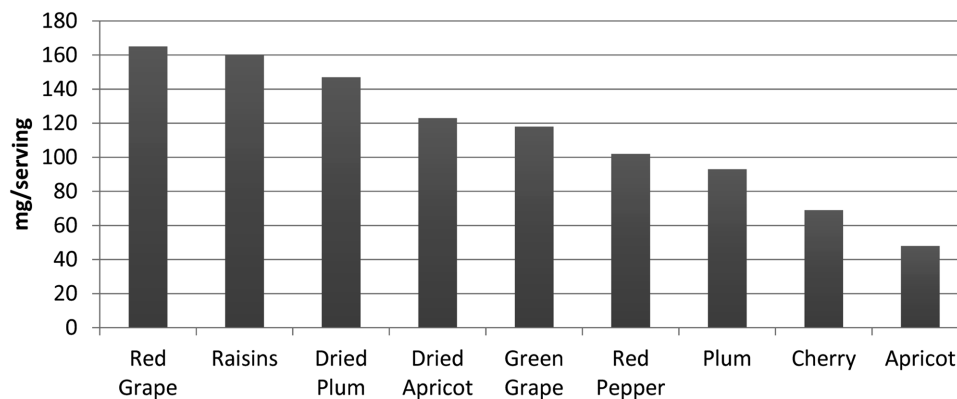


Fig. 1. Total polyphenols in different fruits (per serving) adapted from Karakaya et al.<sup>15</sup>

and inhibited tert-butylhydroperoxide (tBHP)-induced antioxidant cytotoxicity, decreased LDL oxidation and increased apoptosis. The antioxidant activity was correlated to the polyphenolic content.<sup>18</sup> Kelebek assessed the total phenolic and antioxidant activity of three white (Besni beyazi-BBR, Hatun parmagi-HPR and Sultaniye-SR) and two red (Antep karasi-AKR and Besni karasi-BKR) Turkish raisin varieties. Twenty-seven phenolic compounds: four flavan-3-ols, six phenolic acids, four flavonols and 13 anthocyanins were identified and quantified. The most abundant phenolics were: flavanol, (+)-Catechin (range, 5.63-41.9 mg/100 g), phenol acid, trans-caftaric acid (range, 2.05-11.4 mg/100 g), flavonol, quercetin-3-O-glucoside (range, 0.28-1.28 mg/100 g), anthocyanin and malvidin-3-O-(6-O-p-coumaroyl)-glucoside (range, 1.68-2.26 mg/100 g). Antioxidant capacity was 40.74-077.41 mmol Trolox kg<sup>-1</sup> as determined by ORAC assays.<sup>19</sup>

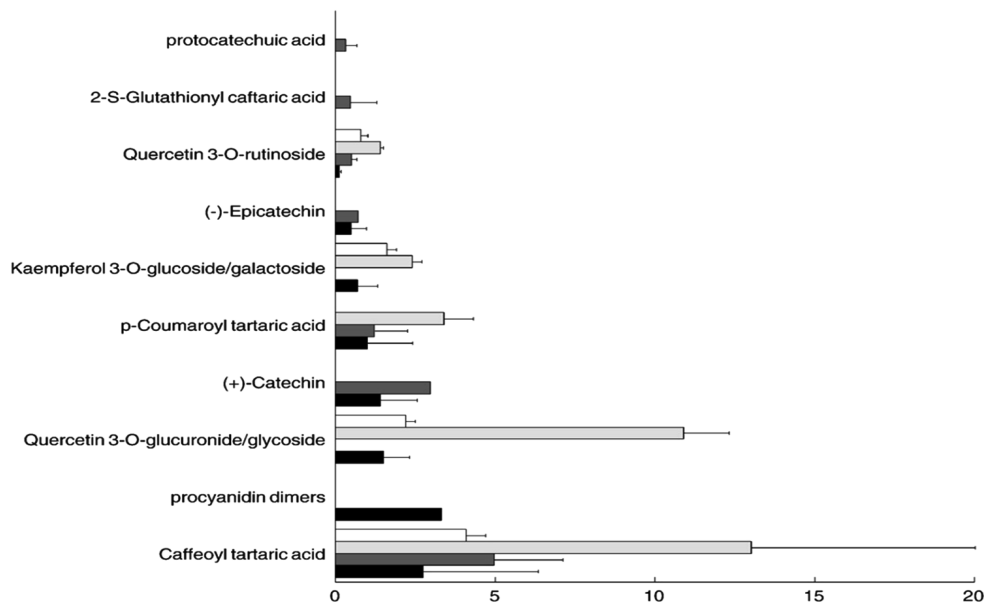
#### Bioavailability

Although the phenolic content and ORAC values of fruit are important, it is equally necessary that the compounds are absorbable and bioavailable. Williamson et al.<sup>10</sup> reviewed the polyphenol, phenolic acid, and tannin (PPT) composition of raisins and predicted their likely bioavailability. Fig. 2 shows the phenolic content of raisins from the USDA nutrient database. Caffeoyl tartaric acid (CTA) and Quercetin 3-0-

glucuronide are both found in high amounts in raisins. They proposed pathways of metabolism and assimilation for Caffeoyl tartaric acid and Quercetin 3-0-glucuronide. In the small intestine Quercetin 3-0-glucuronide is converted to Quercetin in the brush border cells by lactase phlorizin hydrolase, and in the colon, both Caffeoyl tartaric acid and Quercetin 3-0-glucuronide are metabolized by gut microflora.

Parker et al.<sup>20</sup> compared the antioxidant capacity and phenolic content of Thompson seedless grapes in three forms: green grapes, sun-dried raisins and golden raisins. The ORAC values ( $\mu\text{mol TE/g} \pm \text{SD}$ ) of: golden raisins  $104.5 \pm 8.7$ , sun-dried raisins  $37.4 \pm 3.7$  and fresh grapes  $10.8 \pm 0.49$ , were all significantly different ( $p < 0.0001$ ). Fifteen healthy human males consumed 50 g of raisins or 250 g of grapes for 4 weeks in a cross-over design. Although there was no significant change ( $p > 0.05$ ) in total serum phenolics, serum ORAC values increased significantly ( $p < 0.05$ ) for grapes after 2 weeks and golden raisins after 3 weeks. The authors hypothesized that the lack of significant findings may be the result of insufficient raisin consumption in the typical diet to overcome postprandial oxidation effect of high carbohydrate consumption, but raisins may have beneficial antioxidant effects over time.

After consuming 5.5 oz of raisins per day plasma antioxidant capacity was significantly ( $p < 0.05$ ) increased



**Fig. 2.** Polyphenols from raisins have similar bioavailability to those from grapes & wine. Values are mg/100 g "wet" weight.<sup>10</sup> Unshaded bars indicate sun-dried raisins; light gray bars, golden raisins; dark gray bars, raisins; and black bars, green grapes.

as assessed by the FRAP assay, plasma TRAP values were not altered in a study by Barnes et al.<sup>21</sup> The quantity of the bioavailable phenolic compounds in raisins has been assessed by Kanellos et al.<sup>22</sup> Fifteen healthy volunteers consumed 144 g of raisins followed by blood collection at 0 and 1, 2, 3 and 4 hours post consumption. Twenty-five phytochemicals were identified and quantified in raisins; oleanolic acid, a triterpenoid, was found in the highest concentration. Seventeen phytochemicals were found in the plasma: sixteen phenolics and oleanolic acid. Thirteen of the seventeen peaked 1 hour after raisin consumption.

Liu et al.<sup>23</sup> recently determined the chemical identity of bioactive constituents of raisins using bioactivity-guided fractionation. Three novel triterpenoids, were isolated and identified: 3 $\beta$ ,13 $\beta$ -dihydroxy-12,13-dihydrooleanolic acid (DOA), 3 $\beta$ ,12 $\beta$ ,13 $\beta$ -trihydroxy-12,13-dihydrooleanolic acid (TOA), and 3 $\beta$ ,13 $\beta$ -dihydroxy-12,13-dihydrourosolic acid (DUA).

The phenolic compounds present in high amounts in raisins seem to have bioavailability similar to wine and grapes according to Carughi et al.<sup>25</sup> Blood concentration of polyphenols after intake of 100 g of raisins, 400 g of grapes (equivalent amount), and 300 mls of wine, as seen in Fig. 3, is approximately the same.<sup>24,25</sup>

The majority of phenolics in raisins are preserved during processing as seen in the preparation of raisin jam from raisins in study by Rababah et al.<sup>26</sup> Raisin jam was produced by combining 83.6 g whole raisins with 412.8 g water and boiled for a minimum of 30 minutes. Total phenolics for raisins and raisin jam were  $331.6 \pm 12.3$  and  $281.2 \pm 11.9$  mg GAE/100 g

respectively, 85% conserved during processing, and anthocyanins in raisins and raisin jam were  $34.5 \pm 1.6$  and  $23.5 \pm 1.5$  mg cya3-glu/100 g respectively, 68% conserved during processing.<sup>26</sup>

#### Methods for elucidation

Zhao<sup>27</sup> found that pH and extraction solvent affected the phenolic content and antioxidant activity of raisin extract. The type of solvent (methanol, ethanol, or acetone) and solvent/water ratio affected the total phenolic content (TPC); ethanol:water (60:40, v/v) had the highest TPC of 375 mg GAE/100 g. The higher pH5 solvent produced more of the lower molecular weight flavonoids (catechin and epicatechin) and phenolic acids: caftaric acid, gallic acid, protocatechuic acid which had the greatest antioxidant activity. The lower pH3 extract produced more of the higher molecular weight flavonoids: rutin, resveratrol, and kaempferol, which showed poor antioxidant activity. Condensed tannins showed antioxidant activity in some extracts.<sup>27</sup> The variation seen in the reported phenolic content and antioxidant activity of raisins may be due to the method of extraction used.

#### Inflammation and Cancer chemoprevention

##### *In vitro* studies

Due to their high antioxidant content, the anti-inflammatory and cancer chemopreventive effects of raisins have been assessed. Kaliora et al.<sup>28</sup> investigated the anti-inflammatory effect of methanol extracts of four varieties of raisins: three different varieties of currants from Greece (Vostizza,

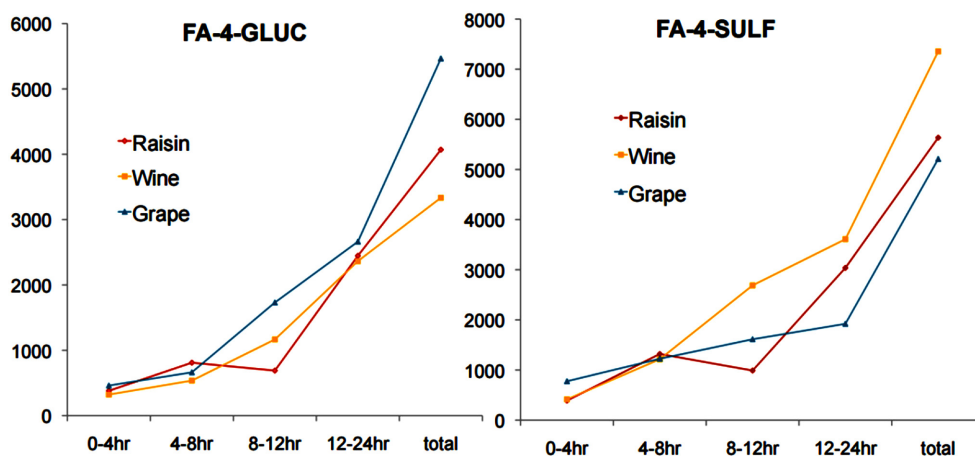


Fig. 3. The amount (pmol) of ferulic acids conjugates (polyphenolic metabolites) in urine after consumption of wine, grapes and raisins<sup>24,25</sup>

Nemea and Messinia) and Sultanas from Crete on gastric cancer cell lines. All four extracts of dried raisins at 500 µg suppressed cell proliferation, the effect was significant for Sultanas ( $p < 0.05$ ) and currants from Nemea ( $p = 0.02$ ). Cretan sultanas, Nemea currants, and Messinia currants at 500 µg dried product/mL significantly increased apoptosis ( $p = 0.03$ ), ( $p = 0.02$ ) and ( $p = 0.03$ ), respectively. Inflammatory markers, protein and mRNA levels of Intercellular Adhesion Molecule 1 (ICAM-1) in Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) stimulated cells decrease significantly ( $p < 0.05$ ) in all four 500 µg extracts. There was no significant ( $p > 0.05$ ) decrease in IL-8 protein levels or IL-8 mRNA.<sup>28</sup>

Kountouri et al.<sup>29</sup> studied the effect of methanol extracts from currants and sultanas on HT29 colon cancer cells. Both extracts decreased cell proliferation and IL-8 levels while NF-kappaB p65 activation was also observed. Antioxidant and anti-inflammatory effects were dose and time dependent. Additionally, both extracts exhibited anti-radical activity *in vitro* as well as cancer preventive efficacy on colon cancer cells. Authors hypothesized the beneficial, anticancer effects may be due to the high content of phenolic compounds.<sup>29</sup>

Weyant et al.<sup>30</sup> also studied the effect of (+)-catechin on intestinal tumor cells using an animal model. Administration of (+)-catechin at 0.1 and 1% decreased intestinal tumor number by 75 and 71% respectively.<sup>30</sup> This compound shows promise as a cancer chemopreventive agent.

Di Lorenzo et al.<sup>31</sup> found mixed results when examining five raisin varieties. Only the Turkish variety showed a decrease in plasma TNF- $\alpha$  induced IL-8 release, which appeared to be related to the presence of seeds in the Turkish variety raisins which were not present in other varieties. The authors concluded that while raisins in general showed activity in decreasing the IL-8 and NF- $\kappa$ B pathway, raisins with seeds exhibited a significant reduction in inflammatory risk factors.<sup>31</sup>

Liu et al.<sup>23</sup> found three novel triterpenoids, DOA, TOA, and DUA which all exhibited anti-proliferative activity against MCF-7/DOX cells. TOA showed the highest activity, with a median effective concentration (EC<sub>50</sub>) value of 3.60 ± 0.55 µM, and the cytotoxic mechanisms of action was investigated by targeting the mitochondrial and protein tyrosine kinase signaling (Ras/Raf/ERK).

#### *In vivo*

Rankin et al.<sup>32</sup> studied the effect of daily raisin con-

sumption on oxidative stress and inflammation. Seventeen overweight men and women consumed 90 g of raisins or an isocaloric placebo (264 kcal/day) for 14 days in a randomized, crossover design while following a low-flavonoid diet. Inflammation and oxidative stress markers were tested pre and post intervention. Consuming raisins moderately increased serum antioxidant capacity as shown by ORAC values, but there was no change seen in inflammatory markers between the intervention and the control.<sup>32</sup>

Conversely, Puglisi et al.<sup>33</sup> found that raisins had a significant effect on plasma lipids and inflammatory cytokines. Following a 2-week run-in period, 17 men and 17 postmenopausal women were randomly assigned to one of three groups: group 1 consumed 1 cup of raisins, group 2 increased the amount of steps walked, and group 3 consumed raisins and increased amount of steps, for 6 weeks. Plasma Interleukin-8 (IL-8) and Monocyte Chemoattractant Protein-1 (MCP-1) did not change in any group; a trend for a decrease was seen in raisins for MCP-1 ( $p = 0.078$ ). Plasma TNF- $\alpha$  was decreased from 3.5 ng/L to 2.1 ng/L in the raisin group ( $p < 0.025$  for time and group × time effect). All subjects had a reduction in plasma ICAM-1 ( $p < 0.01$ ).<sup>33</sup> The lack of consistent findings may be a function of the amount of raisins or raisin extracts administered and the varietal of raisin studied.

#### Fiber and Gut health

The current US recommendation for Adequate Intake of dietary fiber is 38 g for males and 21 g for females (age ≥ 19 years) or 14 g/1,000 calories consumed,<sup>34</sup> and the Korean Adequate Intake for dietary fiber is 12 g/1,000 calories consumed.<sup>35</sup> Current average per capita consumption of dietary fiber in Korean is 12.24 g/1,000 kcals for adults.<sup>36</sup> 2005~2006 National Health and Nutrition Examination Survey (NHANES) data shows that average daily consumption of dietary fiber in the United States is 17.6 g and 13.7 g per day for males and females (age ≥ 19 years) respectively.<sup>37</sup> Average daily consumption of fiber in certain Korean population groups and for the average US adult falls short of the recommendations.

Dried fruit and raisins are good sources of dietary fiber. When the Association of Official Analytical Chemists (AOAC) Analysis Method 2009.01 analytical method was used to determine the fiber content of raisin, which included some of the fermentable fibers, one serving of

raisins contained 10% of the FDA's daily recommended fiber.<sup>38</sup> The current FDA guidelines for listing fiber on the nutrition facts label does not include inulin and soluble fibers, so one serving of raisins (43 g) contains 1.6 g or 6% of Daily Value for fiber.<sup>39</sup>

In 2003 Camire and Dougherty<sup>40</sup> assessed the dietary fiber composition per 100 g of three types of raisins. Soluble fiber composition was 1.42, 1.52, and 1.76, insoluble fiber composition was 3.63, 3.85, and 3.29, and total fiber composition was 5.05, 5.37 and 5.05, for natural sun-dried (SDR), artificially dried (dipped), and sulfur dioxide treated (golden) raisins g/100 g, respectively.<sup>40</sup>

Spiller et al.<sup>41</sup> evaluated the effect of dietary fiber from sun-dried raisins on colonic function, bile acid content, and volatile fatty excretion in healthy adults in a crossover design study. For nine weeks, thirteen healthy subjects were daily fed 120 g of sun-dried raisins or 5 g of cream of tartar, which is equal to the tartaric acid content in raisins. Intestinal transit time was 42 hours on the baseline diet, 31 hours on cream of tartar diet, and 28 hours on the sun-dried raisin diet ( $p > 0.05$ ). Sun-dried raisins increased fecal wt. ( $p < 0.05$ ), with no change seen with the cream of tartar diet. Total bile acid concentration decreased from 1.42 to 1.09 mg per day with sun-dried raisins ( $p < 0.05$ ), while no change was seen with cream of tartar subjects. Total short chain fatty acid excretion measures increased from 5.6 to 7.6 g for 4 days with sun-dried raisin diet.<sup>41</sup>

Another study also by Spiller et al.<sup>42</sup> assessed the effect of SDR on intestinal transit time. Sixteen healthy adults were studied in three cycles of two weeks each. Subjects consumed 84, 126, or 168 g of SDR per day. Fecal weight increased from 168 g  $\pm$  14 g per day without raisins at baseline to 200 g  $\pm$  24 g per day with consumption of 168 g per day of raisins. Transit time decreased from 54  $\pm$  6 hours without raisins to 42  $\pm$  6 hours with consumption of 168 g of raisins.<sup>42</sup>

Although fructans are not included in the FDA definition of fiber,<sup>43</sup> raisins are a good source providing over 5 g of fructans per 100 g. Fructans, not found in grapes, are created through the drying process of producing raisins.<sup>40</sup> Fructans have been shown to improve gut microflora by increasing bifidobacteria and lactobacilli and possibly decreasing CVD risk through reduction of triglyceride and cholesterol levels.<sup>44</sup>

Mandalari et al.<sup>45</sup> assessed the effect of SDR on *in vitro* composition of gut microbiota using a full model of a

human gastrointestinal tract which included simulated mastication and dynamic gastric, duodenal and colonic models. They assessed bacterial counts at 0, 4, 8, and 24 hours after the addition of either raisins or fructooligosaccharides compared to a control. At 24 hours the beneficial lactobacilli bacteria increased in the raisin and fructo-oligosaccharides (FOS) conditions. Final counts of lactobacilli at 24 hours of fermentation were  $2.24 \times 10^7$  colony forming units (CFUs) lactobacilli per  $\text{ml}^{-1}$  for the control,  $1.51 \times 10^8$  CFUs lactobacilli for the SDR, and  $1.86 \times 10^9$  CFUs lactobacilli for the FOS.<sup>45</sup>

Wijayabahu et al.<sup>46</sup> conducted a raisin feeding study in 13 adult subjects. Subjects consumed one ounce of raisins, three times a day for fourteen days; adherence to the study protocol was high. Fecal samples were collected at the beginning, middle and end of the study period and gut microbiota composition was assessed. A significant reduction in the potentially pathogenic, *Klebsiella* species was observed from baseline to day fourteen. These findings suggest that raisins may provide a potential benefit by reducing enteric inflammation.<sup>46</sup>

### Diabetes and Glycemic control

The American Diabetes Association defines diabetes/diabetes mellitus as "a group of diseases characterized by high blood glucose levels that result from defects in the body's ability to produce and/or use insulin".<sup>47</sup> Glycemic Index (GI) describes the effect of carbohydrate consumption on blood glucose levels.<sup>48</sup> Although there isn't a standard serving size for raisins, 2 tablespoons of raisins is one (fruit) exchange in the diabetic exchange list. One exchange or serving of raisins is about 15 grams of carbohydrate and 60 calories.<sup>49</sup>

Esfahani et al.<sup>48</sup> found the glycemic index for raisins was 49 based on the glucose scale. Previous reports of glycemic index for raisins have ranged from 49~64. This discrepancy may be due to the populations that were studied. Jenkins et al.<sup>50</sup> first reported the GI of raisins to be 64 from a study with only six subjects.<sup>50</sup> More recently a study by Kim et al.<sup>51</sup> reported GI values of 49 in sedentary individuals, 49 in individuals with prediabetes and 55 in aerobically trained adults. Bell<sup>52</sup> determined raisins to have a low to moderate GI based on the studies available, which at that time it was a reasonable assessment.<sup>52</sup>

To determine a standard GI reference for raisins, Esfahani et al.<sup>48</sup> conducted a partial randomized, crossover design

study using standard GI methodology (ISO 26642:2010; International Organization for Standardization). Subjects were four males, six females with a mean age of 39 (SD 11) years and an average BMI of 26.4 (SD 6.2) kg/m<sup>2</sup>. Blood was drawn for each subject on four separate days over a period of 2~8 weeks after a 10~14 hour overnight fast. Participants were instructed to maintain stable dietary and activity habits throughout the study. Samples were collected via finger-stick blood at 15, 30, 45, 60, 90 and 120 min. The glycemic index was determined to be low at 49. The low GI may be partially explained by the fiber content and sucrose and fructose ratio, which may enhance hepatic glucose uptake,<sup>49</sup> and the polyphenols, phenolic acid, tannins, antioxidants, flavonoids, and resveratrol content of raisins.<sup>10,53</sup>

Oetl  et al.<sup>54</sup> compared processed snack meals and whole-food snack meals in 10 healthy participants. The areas under the insulin curve were 68% higher after the candy-bar than after a raisin-peanut snack, 75% higher after a cola drink with crisps and 52% higher after a banana-peanut snack.<sup>54</sup>

Kanellos et al.<sup>55</sup> analyzed the effect of raisin consumption on fasting glucose, glycated hemoglobin (HbA<sub>1c</sub>), antioxidant status, and blood pressure in individuals with T2DM. Subjects were instructed to consume two fruit servings of raisins (36 g/d) in place of a snack with similar energy density. The comparator snack was not defined. A significant ( $p < 0.05$ ) reduction was seen in diastolic blood pressure and an increase in total antioxidant potential in the raisin group compared with control. No significant differences were seen in fasting glucose or HbA<sub>1c</sub> between the two groups.<sup>55</sup>

Bays et al.<sup>56</sup> conducted a crossover design study of pre-diabetics at the Louisville Metabolic and Atherosclerotic Research Center (L-MARC) comparing the effect of raisin snacks to equal caloric refined grain snacks three times per day on CVD risk factors. There was a 36 mg/dL (23%) decrease in postprandial blood glucose, 32 mg/dL (19%) decrease in fasting glucose, and a 0.12% decrease in HbA<sub>1c</sub> levels in the raisin group compared with the control. This study also showed improvements in systolic blood pressure.<sup>56</sup> The reason for the partial incongruent findings between Bays<sup>56</sup> and Kanellos<sup>55</sup> might be the specificity of the comparator snack. Bays described the comparator snack to be a highly-refined carbohydrate and Kanellos did not give any description of the raisins replacement. If the

raisins were substituted for a fruit snack a significant difference would not necessarily be expected.

The phytonutrients in raisins may protect against developing diabetes. In a study on T2DM and glycemic response to grapes or grape products, Zunino<sup>57</sup> found that grapes and products derived from grapes may protect against inflammation related to T2DM. Resveratrol, quercetin, catechins and anthocyanins have potential for reducing hyperglycemia, improving pancreatic  $\beta$ -cell function and protecting against  $\beta$ -cell loss.<sup>57</sup>

### Cardiovascular disease and Raisins

According to the American Heart Association, heart disease describes a range of conditions that affect the heart and is often used interchangeably with the term cardiovascular disease (CVD).<sup>58</sup> Polyphenols in raisins appear to reduce the absorption of cholesterol and also decrease plasma triglyceride concentrations.<sup>9</sup>

Puglisi 2008<sup>33</sup> found that consuming 1 cup raisins/day + increased walking produced a significant decrease in: systolic blood pressure ( $p = 0.008$ ), plasma total cholesterol by 9.4% ( $p < 0.005$ ), plasma LDL cholesterol, 13.7% ( $p < 0.001$ ). This decrease in LDL cholesterol was explained by a significant ( $p < 0.001$ ) increase in lipoprotein receptor messenger RNA abundance.<sup>59</sup>

Barnes et al.<sup>21</sup> assessed the effect of raisins on oxidized LDL in subjects, ( $n = 32$ ) that were randomly assigned into three groups and consumed either 2, 3.5, or 5.5 ounces of raisins per day for four weeks. Blood samples were drawn at baseline, 2, and 4 weeks, plasma antioxidant levels and circulating oxidized LDL levels were measured. Data were analyzed using the Tukey all pairwise comparison and Tukey-Kramer tests. Circulating oxidized LDL levels decreased significantly ( $p < 0.05$ ) after 4 weeks with 3.5 oz. raisins/day and after 2 weeks with 5.5 oz. raisins/day.<sup>21</sup>

In animal model studies by Abdel-Hamid and Ayuob,<sup>60</sup> raisins have shown a cardioprotective effect. Wister rats ( $n = 40$ ) being fed a high cholesterol diet (HCD) were randomly divided into four groups ( $n = 10$ ): control, raisin-fed, HCD-fed and HCD +raisin fed group. At 13 weeks the animals were sacrificed, hearts were dissected and a histopathological examination and blood analysis was performed. Raisin administration with HCD significantly ( $p < 0.05$ ) decreased low density lipoprotein levels from ( $86.59 \pm 1.2$  mg/dl to  $34 \pm 3.8$  mg/dl) compared to the HCD alone. Blood glucose, insulin, cholesterol, and triglycerides

all decreased significantly ( $p < 0.05$ ) in the raisin+HCD compared to the HCD alone, while high density lipoprotein levels increased ( $18.4 \pm 2.1$ , to  $25.9 \pm 1.3$  mg/dl). Positive histological changes were also seen: decreased cardiomyocytes' degeneration, cellular infiltration, hemorrhages and blood vessels affection. Immunohistochemical findings were seen with the HCD+raisins: reduced fibrosis by decreasing the immunoexpression of alpha smooth muscle actin marker and significantly increased immuno-expression of endothelial nitric oxide synthase.<sup>60</sup>

A study by Anderson et al.<sup>61</sup> conducted at the L-MARC compared the effect of consuming either 90 calories of raisins or an alternative high carbohydrate snack, three times per day, on cardiovascular risk factors in mildly hypercholesterolemic or hypertensive subjects. The CVD risk factors studied were systolic blood pressure, diastolic blood pressure and waist circumference. Of the risk factors studied, those that changed significantly from baseline to week 12 of the study were: systolic blood pressure [-4.8% to -7.2% (-6.0 to -10.2 mmHg)], and diastolic pressure [-2.5% to -6.4% (-2.4 to -5.2 mmHg)]. There was a non-significant ( $p > 0.05$ ) decrease in waist circumference of 0.4% in the raisin group. This same study showed significant improvement in 2-hour postprandial glucose (-13 mg/dL) and HbA<sub>1c</sub> (-0.12%) in the raisin group. The difference in blood pressure may be partially explained by the large difference in potassium content between groups. Raisins and high carbohydrate snacks contained 220 mg and 23 mg per serving respectively.<sup>61</sup>

Bruce et al.<sup>62</sup> assessed the effect of a high phytochemical-rich (HPC) diet including three 42 g boxes/d of raisins versus a refined-food diet on serum antioxidants and lipoproteins. In a direct crossover design study, women with hyperlipidemia ( $n = 12$ ) consumed a refined diet for 4 weeks followed by the HPC diet. There was a decrease in serum lipids in the HPC diet, total cholesterol 13% ( $p < 0.05$ ) and LDL cholesterol 16% ( $p < 0.001$ ).<sup>62</sup>

### Energy and Exercise performance

Raisin consumption has been shown to improve athletic performance. Sacheck et al.<sup>63</sup> compared the effect of three isocaloric snacks in 115 young soccer players (ages 9.01  $\pm$  0.9) including: a raisin/nut bar, a peanut butter graham bar or a rice cereal bar. Following a 50 minute game of moderate to vigorous activity, the only difference subjects reported was more feelings of fatigue was associated with

consuming the rice cereal (high sugar, low flavonoid) bar while results for the other two bars were not significantly different.<sup>63</sup>

Kern et al.<sup>64</sup> compared the effect of commercial carbohydrate supplements and raisins on cycling performance. Forty-five minutes prior to exercise, participants (four males, four females) were randomly given a pre-determined amount (1 g carbohydrate per kilogram body weight) of either sports gels or raisins. Participants then completed a 45-minute constant intensity ride followed by a 15-minute performance ride. Researchers found no difference in performance between sports gels and raisins and concluded that sports gels and raisins produce equal work output.<sup>64</sup>

Endurance athletes have been known to use a wide variety of carbohydrate supplements like gels, shots, bars and chews. However, natural foods that are high in carbohydrate can offer the same benefits during sports performance as commercial carbohydrate supplements. Rietschier et al.<sup>65</sup> studied the effects of sun-dried raisins and sports jelly beans as carbohydrate supplements during 10K time trials. Participants (10 male cyclists) were asked to complete a 2-hour glycogen depletion period followed by a 10K time trial. During the time trial, cyclists were given 1 of 2 carbohydrate supplements (sports jelly beans or sun-dried raisins). The results showed no significant difference between 10K time trials for the sports jelly beans or the sun-dried raisins.<sup>65</sup>

A third study by Too et al.<sup>66</sup> conducted at the University of California Davis tested the effect of sun-dried raisins vs. sports chews in running performance. Eleven male runners completed an 80-minute glycogen depletion, exercising at 75% VO<sub>2</sub>max, followed by a 5K timed trial. The participants completed the trial in all three conditions (trials with water, raisins, and sport chews) separated by seven days. The researchers found no significant difference between sun-dried raisins and sports chews for the time to complete the 5K. Times to complete the 5K were  $20.6 \pm 2.6$ ,  $20.7 \pm 2.5$  and  $21.6 \pm 2.7$  min for raisins, chews, and water respectively. Times were significantly shorter ( $p \leq 0.05$ ) for both raisins and chews compared to the water control.<sup>66</sup>

Nutritional analysis by Apfel et al.<sup>67</sup> comparing raisins to sports chews showed that carbohydrate, sugar, fiber, protein and carbohydrate content was 96 g, 80 g, 6.4 g and 3.2 g respectively for raisins while content of the sports chew was 96 g, 48 g, 0 g and 0 g respectively. The mineral



content of the raisins was 32 mg sodium, 952 mg potassium, 68 mg calcium, 44 mg magnesium, 136 mg phosphorus and 8 mg folate. The sports chews contained 280 mg sodium, 80 mg potassium, and 0 mg calcium, magnesium, phosphorus and folate. The vitamin content of raisins was 3.2 mg vitamin C, 4.8 mg vitamin K and 16 mg vitamin E while the sports chews were void of these vitamins. Overall raisins provided a more nutrient dense alternative to sports chews.<sup>67</sup>

An additional study by Byrne et al.<sup>68</sup> supports the use of raisins in exercise, as well as in an impaired fasting glucose population. The researchers analyzed serum glucose and insulin responses to three pre-exercise snacks before, during and after exercise. Twenty men with and without impaired fasting glucose participated in this study. The snacks compared were a natural fruit snack of raisins, an energy bar or a glucose solution. This study aimed to determine if the natural snack would yield more desirable glucose and insulin concentrations than the other snacks. Glucose concentrations were higher in the impaired fasting glucose group with all snacks. The energy bar snack reduced glycemia but not insulinemia and the raisins lowered both the postprandial glycemic and insulinemic responses compared to the glucose solution.<sup>68</sup>

Kalman et al.<sup>69</sup> compared the effects of isocaloric snack of raisins versus granola bars on feelings of energy in mothers over a 14-day study period. Moms reported a significant increase in energy when they consumed raisins and granola bars as snacks; when comparing the two snacks, raisins were associated with higher energy scores for 13 of 14 test days ( $p = 0.002$ ). Neither snack showed a change in subject weight.<sup>69</sup>

Raisins may provide a less expensive, more nutrient dense, yet equally effective, source of energy during endurance exercise.

### Satiety

Raisins contribute to dietary nutrient density and may increase satiety compared to other commonly consumed snacks. Patel et al.<sup>70</sup> measured *ad libitum* consumption of a variety of snacks, in children ages 8–11 years old. After receiving standardized breakfasts, morning snacks and lunches, children were randomly offered one of four snacks: raisins, grapes, potato chips or chocolate chip cookies, and told to eat until comfortably full. Satiety measured before and at 15, 30, and 45 min after snack

consumption showed that children consumed the least calories from grapes and raisins and the greatest from cookies. Snacking on grapes and raisins also led to lower cumulative food intake (calories of all meals combined) compared to other snacks, while grapes also lowered appetite compared to all other snacks.<sup>70</sup>

Patel et al.<sup>71</sup> studied the effect a pre-meal snack containing raisins on total calorie intake in children. In experiment 1, participants received either an *ad libitum* snack (grapes, raisins, almond and nut mixture or water control) and then were offered an *ad libitum* pizza meal. In experiment 1, children consumed significantly lower cumulative calories when consuming raisins and water compared to grapes and nut/raisin mixture. In experiment 2, participants were offered a 150-calorie snack (grapes, raisins, almond and raisin mixture or water control) which was followed by an *ad libitum* pizza meal. In experiment 2, children consumed lower cumulative calories after consuming raisins and water. The authors concluded that a pre-meal snack of raisins reduced total calories consumed at a meal and did not increase cumulative energy intake.<sup>71</sup>

### Raisins and Dental health

Raisins have been thought to be important in the etiology of dental caries because of high sugar content and suspected stickiness. Yet three conditions are required to promote dental caries: low oral pH, food sticking to teeth, and active cariogenic bacteria in the biofilm.<sup>72</sup> Rivero-Cruz<sup>73</sup> and Wu et al.<sup>74</sup> assessed the antimicrobial agents of Thompson's seedless raisins against select oral pathogens. Eight compounds derived from raisins that are known to have oral antimicrobial effect were studied *in vitro* to determine their individual antimicrobial effects. They were assessed as to their impact on *Streptococcus mutans* (*S. mutans*) and *Porphyromonas gingivalis* (*P. gingivalis*). The compounds oleanolic, oleanolic aldehyde, and 5-(hydroxymethyl)-2-furfural were active against *P. gingivalis*, and those three compounds are found on the skin of grapes and raisin; in addition to rutin which was effective against *S. mutans*.<sup>73</sup>

Wu<sup>74</sup> assessed the effects of grapes on oral health in an *in vitro* and an *in vivo* study. *In vitro* grape seed extract reduced demineralization in artificial root carie lesions. *In vivo* oleanolic acid suppressed adherence of *S. mutans* biofilms. *In vivo* raisins and raisin containing bran cereal did not reduce plaque pH below 6.0 in 7–11 year old

subjects.

Utreja et al.<sup>75</sup> conducted a randomized control study in twenty 7–11 year old children studying the effects of raisin bran flakes, commercial raisin bran cereal and experimental raisin bran cereals. The positive control was 10% sucrose and the negative control was 10% sorbitol. Levels of pH were measured at 2, 5, 10, 15 and 20 min. Results of this study found that consumption of raisins and experimental raisin bran did not reduce pH below 6.0 over the 30-minute testing period, while bran flakes and sugar-coated raisin bran flakes significantly reduced the pH after ten min.<sup>75</sup>

Issa et al.<sup>76</sup> conducted research on the enamel demineralization properties of eight different whole and juiced fruits and vegetables. Although the differences in demineralization were not significant between products, raisins had the lowest amount of demineralization of all test foods.<sup>76</sup>

Wong et al.<sup>72</sup> conducted a review of literature on raisins and oral health. This study found that raisin consumption did not lower oral pH less than 5.5 and consuming raisins suppressed *S. mutans*. In addition, raisins even though they are rated by consumers as being a “sticky” food, do not stick to teeth and are cleared from the mouth.<sup>75,77</sup>

Hindi et al.<sup>78</sup> investigated the antimicrobial activity of black raisins against gram positive and gram negative bacteria and yeast. Gram positive bacteria included: *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae*. Gram negative bacteria included: *Pseudomonas aeruginosa*, *Salmonella typhi*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Acinetobacter*, *E. coli*, and *Serratia* spp. In the study, petri dishes were prepared for analysis of the adhesion of bacteria on oral epithelial cells. In addition, a biofilm formation assay was used to determine the anti-biofilm properties of raisins. There was an inverse correlation between raisins and gram negative bacteria. The active components of black raisins that are effective in inhibition of *E. coli* bacteria include: Catechin/ Flavonoids, Gallic acid/ Phenolic acid, and Protocatechuic acid. Flavonoids, also found in raisins, inhibit *Bacillus*, *Shigella*, *Salmonella*, *Vibrio*, and *E. coli* species. In addition, Ferulic acid/ Phenolic acid inhibit *E. coli* and *Salmonella* spp, Protocatechuic acid inhibits *E. coli* spp.<sup>78</sup> Although raisins show antibacterial activities *in vitro* and against oral pathogens, raisins do not exhibit anti-adherence properties against *E. coli* in the urinary tract as demonstrated with other dried fruits.<sup>79</sup>

### Choking hazard

Raisins have been considered a choking hazard by many groups, including the American Academy of Pediatrics (AAP) until their review in 2011<sup>80</sup> when they removed raisins from the list of choking hazards. It seems odd that raisins were ever considered a choking risk as their small size, irregular shape and malleable texture does not match the AAP’s statement that “choking is most commonly caused by any solid, round, cylindrical, or conforming object that has the same diameter as and fits easily into a child’s upper airway”.<sup>80</sup> In 2008 Altkorn et al.<sup>81</sup> published data from twenty six US and Canadian hospitals concerning aspiration and choking. Raisins were not reported as a cause; peanuts and hot dogs caused the highest frequency of injury and mortality, respectively.<sup>81</sup>

### Observational Data on Raisins and Human Health

Keast and colleagues,<sup>82</sup> analyzed the NHANES 1999–2004 adult data and found that 7% of the population consumes dried fruit. Dried fruit consumers, defined as consuming (1/8 cup -equivalent fruit or more per day), had significantly higher Healthy Eating Index scores (measured with the Healthy Eating Index-2005) than non-consumers, with significantly ( $p < 0.01$ ) greater consumption of dietary fiber (+6.6 g/d), vitamins A (+173 µg retinol activity equivalent per day), E (+1.5 mg α-tocopherol per day), C (+20 mg/d), and K (+20 mg/d), calcium (+103 mg/d), phosphorus (+126 mg/d); magnesium (+72 mg/d), and potassium (+432 mg/d). In addition, dried fruit consumers ate less solid fats, alcohol, and added sugars. Dried fruit consumers were also found to have lower BMIs and waist circumferences.<sup>82</sup>

McGill et al.<sup>83</sup> analyzed the 2003–2008 NHANES data for children ages 2 to 19 years ( $n = 9,622$ ) and adults 20+ years ( $n = 12,251$ ) found that consumers of grape products (grapes, raisins and grape juice) had higher Healthy Eating Index-2005 scores and higher intake of total and whole fruit along with lower intakes of solid fat, added sugar, and calories compared with non-consumers. Adult consumers of grape products consumed more total and dark green/orange vegetables. For both adults and children, grape product consumers consumed significantly more of the shortfall nutrients for Americans: dietary fiber, calcium and potassium and other key nutrients: vitamin A, C, and magnesium.<sup>83</sup>

Raisin have been shown to be associated with improved

diet quality and nutrient intake when consumed with other grape products or dried fruits. Fulgoni et al.<sup>84</sup> examined raisin consumption alone in adults using data from NHANES 2001~2012. Raisin consumers (n = 458, 60.1% female) were defined as reporting consumption of any amount of raisins during the first 24-hour diet recall. Consumers compared to non-consumers had higher total Healthy Eating Index scores ( $61.4 \pm 1.0$  vs.  $49.1 \pm 0.2$ ) and lower BMIs ( $27.3 \pm 0.4$  vs.  $28.8 \pm 0.1$  kg/m<sup>2</sup>) and waist circumferences ( $94.1 \pm 0.1$  vs.  $97.8 \pm 0.2$  cm) respectively. The nutrients of concern for under consumption were higher in the raisin consumers vs non-consumers: dietary fiber ( $22.1 \pm 1$  vs.  $16.5 \pm 0.1$  g/d) and potassium ( $3,084 \pm 77$  vs.  $2,665 \pm 10$  mg/d) respectively, calcium and vitamin D were not significantly different. Intakes for raisin consumers were higher than non-consumers for: vitamin C ( $117 \pm 8$  vs.  $94.4 \pm 1.2$  mg/d), vitamin E ( $8.9 \pm 0.5$  vs.  $7.3 \pm 0.1$  mg AT/d), and magnesium ( $355 \pm 11$  vs.  $290 \pm 1$  mg/d) respectively, and lower for intakes of saturated fatty acids ( $21.2 \pm 0.9$  vs.  $25.0 \pm 0.1$  g/day), added sugars ( $14.9 \pm 0.7$  vs.  $18.0 \pm 0.2$  tsp equivalents/day), and sodium ( $3,190 \pm 78$  vs.  $3,541 \pm 17$  mg/day) respectively. Adult raisin consumers were 39% less likely [odds ratio (OR): 0.61, 99th confidence interval (CI): 0.41, 0.89] to be overweight or obese.<sup>84</sup>

### Raisins and Children

Raisin consumption among children (2~18 years of age) has also been linked to health benefits.<sup>85</sup> Fulgoni et al. defined raisin consumers (n = 154) as those who consumed any amount of raisins during a 24-hour period. The Healthy Eating Index-2010 scores among consumers were higher than non-raisin consumers ( $55.5 \pm 1.7$  vs.  $45.1 \pm 0.3$ ) respectively. The largest differences in sub-component scores for raisin consumers as compared to non-consumers were for calories from solid fats, added sugars, and alcohol, ( $13.7 \pm 0.8$  vs.  $10.2 \pm 0.1$ ) and whole fruit ( $3.8 \pm 0.2$  vs.  $2.1 \pm 0.04$ ). Additionally, nutrients of concern for under consumption in children: dietary fiber ( $16.3 \pm 0.8$  vs.  $13.2 \pm 0.1$  g/d), magnesium ( $255 \pm 7$  vs.  $228 \pm 1$  mg/d), and potassium ( $2,578 \pm 110$  vs.  $2,221 \pm 15$  mg/d) were significantly higher in raisin consumers compared to non-consumers respectively. Added sugar, a nutrient of public health concern for overconsumption was lower among raisin consumers compared to non-consumers ( $15.7 \pm 1.1$  vs.  $19.7 \pm 0.2$  tsp equivalents).<sup>85</sup>

Additionally, recent data analysis of NHANES 2001~2012 data by Fulgoni et al.<sup>86</sup> showed that consumption of

raisin-containing foods (RCFs) was associated with higher nutrient intake and diet quality in children and adults. Most notable, Healthy Eating Index-2010 diet scores were higher in RCFs consumers vs. non-consumers ( $58.6 \pm 0.6$  vs.  $54.3 \pm 0.4$ ) and ( $50.0 \pm 0.5$  vs.  $45.5 \pm 0.2$ ) for adults and children respectively. Dietary fiber and potassium were significantly higher while saturated fat and sodium was significantly lower for RCFs consumers, vitamin A, folate, iron and magnesium intakes were all significantly higher for adult consumers.<sup>86</sup>

Raisins have some of the highest polyphenolic content and antioxidant ORAC levels compared with traditional dried fruits and compare favorably with many other fruits as well.<sup>11-17</sup> Many of the polyphenols in raisins are well assimilated and bioavailable.<sup>10,18-27</sup> Raisins have sufficient fiber to reduce transit time and positively affect gut microbes.<sup>38-46</sup> Raisins reduce risk factors for CVD and T2DM, total and LDL cholesterol, blood pressure and blood sugar compared to carbohydrate controls.<sup>9,21,33,54-62</sup> Raisins improve athletic performance compared to a water control and perform equal to sports energy gels, shots and jelly beans at producing sustained energy during long term athletic competitions.<sup>63-69</sup> Although the effect of raisins on inflammatory markers is mixed, the cancer chemopreventive effects *in vitro* studies on cancer cell lines is promising.<sup>23,28-33</sup> Raisins produce an oral environment that is non-cariogenic and do not fit the APP criterion for a choking hazard.<sup>71,73-78,80</sup>

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