***Research Article***

**SOURSOP FRUIT (*ANNONA MURICATA* LINN) DOES NOT INCREASE**

**SERUM POTASSIUM LEVELS AND NOT SIGNIFICANT IN**

**CARDIOVASCULAR RISK IMPROVEMENTS**

***RCT Study, Cohort, Epidemiology***

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**Abstract**

Patients with chronic kidney disease tend to have hyperkalemia. They worry about the consumption of fruit for fear of increased serum potassium levels and therefore require a restricted potassium diet. Soursop fruit is thought to be beneficial for chronic kidney disease and cardiovascular risk. What is the effect of soursop fruit supplement consumption on serum potassium levels and cardiovascular risk? This epidemiological research was conducted in Mlati, Sleman, Indonesia. There were 143 samples that conform to the inclusion and exclusion criteria subsequently randomized to two groups. Group I was given 2x100 g/day of soursop and group II was without soursop. A laboratory examination was conducted of potassium, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride levels at weeks 0, 7, and 13 both in the soursop and non-soursop groups. Regular soursop consumption was evaluated every two weeks for three months. Data analysis was performed using an independent *t* test, a nonparametric Mann–Whitney test, and a chi-square test. There was no significant difference in serum potassium levels at week 7 and 13(*p*=0.073 and *p*=0.108). There was also no difference in total cholesterol (*p*=0.254 and *p*=0.932), LDL (*p*=0.221 and *p*=0.710), HDL (*p*=0.400 and *p*=0.960), triglycerides (*p*=0.423 and *p* = 0.580) between the soursop and non-soursop groups. The consumption of soursop fruit at 2x100 g/day has no significant effect on serum potassium levels, so it is safe for those with chronic kidney disease. There was no significant improvement in cardiovascular risk (total cholesterol, LDL, HDL, triglycerides), but in subjects with hypercholesterolemia and hypertriglyceridemia, the mean cholesterol and triglyceride levels decreased at week 7 and 13 compared to no soursop consumption.

Abstrak

Pasien penyakit ginjal kronik cenderung mengalami hiperkalemia. Mereka khawatir konsumsi buah karena takut kalium darahnya naik, oleh karena itu perlu restriksi diet kalium. Buah sirsak diduga bermanfaat untuk penyakit ginjal kronik dan risiko kardiovaskular. Bagaimana pengaruh pemberian minuman suplemen buah sirsak terhadap kadar kalium darah dan risiko kardiovaskular? Penelitian epidemologi di wilayah Mlati, Sleman, Indonesia. Didapatkan 143 sampel yang memenuhi kriteria inklusi dan ekslusi. Selanjutnya diacak menjadi 2 kelompok, kelompok I diberikan perlakuan 2x100 g/hari suplemen buah sirsak dan kelompok II tanpa perlakuan. Dilakukan pemeriksaan laboratorium Kalium, Kolesterol total, LDL, HDL, Trigliserida pada minggu 0,7,13 baik pada kelompok sirsak dan non sirsak. Evaluasi kepatuhan konsumsi sirsak setiap 2 minggu selama 3 bulan. Analisis data menggunakan Independent T-Test, Nonparametrik Mann-Whitney Test, Chi-Square Test. Tidak ada perbedaan bermakna pada kadar Kalium darah minggu 7 dan 13 (p=0,073 dan p=0,108), Kolesterol total (p=0,254 dan p=0,932), LDL (p=0,221 dan p=0,710), HDL (p=0,400 dan p=0,960), Trigliserida (p=0,423 dan p=0,580) antara kelompok sirsak dan non sirsak. Konsumsi buah sirsak 2x100 g/hari tidak berpengaruh signifikan terhadap kadar kalium darah dibanding tanpa konsumsi, sehingga aman dan bermanfaat pada penyakit ginjal kronik. Tidak berbeda bermakna dalam memperbaiki risiko kardiovaskular (Kolesterol total, LDL, HDL, Trigliserida). Tetapi pada subyek dengan hiperkolesterol dan hipertrigliserida rerata kadar kolesterol dan trigliserida turun pada minggu 7 dan 13 dibanding tanpa konsumsi sirsak.

**Keywords**: soursop, potassium, hyperkalemia, chronic kidney disease, cardiovascular.

**INTRODUCTION**

Many patients with chronic kidney disease assume that the consumption of fruit will increase serum potassium levels. Consumption of fruits that contain lots of potassium (apricots and bananas) causes hyperkalemia,1 especially in patients with impaired renal function. Hyperkalemia can lead to serious cardiac arrhythmias and death.2

Several studies have suggested that soursop (*Annona muricata* Linn) consumption is beneficial for kidney disease.3 Surveys-based studies have been conducted in various places including Peru4 and Bolivia5 on the use of soursop in the traditional treatment of kidney disease. Sja'bani (2014) in his report the consumption of 2x100 g/day soursop juice in patients with chronic kidney disease in Yogyakarta, Indonesia can decrease uric acid, serum ureum and creatinine, without causing negative effects.6

The potassium content of soursop fruit is 278 mg/100g.3 The recommended intake of potassium in a standard diet is 4.7 g/day (120 mmol/day); for mild to moderate chronic kidney disease it is < 4.7 g/day, and for severe chronic kidney disease (including those undergoing dialysis) it is < 3 g/day (< 77 mmol/day).7 Soursop consumption of 2x100 g/day is equivalent to 556 mg/day of potassium, this is well below the recommended dietary amount for mild to severe chronic kidney disease, even for those undergoing dialysis. Is the consumption of soursop fruit in patients with mild to severe chronic kidney disease (undergoing hemodialysis) still safe? What is the effect of a soursop fruit supplement on serum potassium levels?

Cardiovascular disease has become a trend in medical talks in both developed and developing countries. Cardiovascular death by 31% from overall mortality rates,8 otherwise, mortality rates due to infection tend to decrease. Various attempts have been made to reduce mortality due to cardiovascular disease by controlling blood pressure, diabetes, dyslipidemia, and even uric acid.

Hypertension is a major risk factor for increased morbidity and mortality due to cardiovascular, cerebrovascular, and end-stage renal failure.9 Within 5 years, prehypertension increases the risk of cardiovascular disease by 45% compared to normal blood pressure.10 Once the importance of prehypertension became known, the ACC/AHA 2017 grouped it into stage I hypertension.11

Soursop fruit is expected to reduce blood pressure, decrease uric acid, and improve cardiovascular conditions by lowering cholesterol, LDL, and triglycerides and increasing HDL.12,13 Soursop fruit contains tannins,14 which play a role in the reduction of triglycerides.15 Soursop fruit also contains flavonoids,13 which can inhibit the activity of the HMG-CoA reductase enzyme in the cholesterol synthesis process. This is the necessary for in-depth research (randomized controlled trials, or RCTs) to determine the effect of soursop fruit supplementation compared to control serum potassium levels and cardiovascular risk.

**MATERIALS AND METHODS**

This study represents in-depth epidemiology research on the effect of soursop fruit consumption in prehypertension with high normal uric acid. Prior to the study, the research design was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Gadjah Mada University – Dr. Sardjito General Hospital Yogyakarta. After being given information about the study, subjects were asked to fill out and sign a willingness to participate form (informed consent).

Data was taken from Mlati Study 10 years ago; the selected subjects still have prehypertension, are 30–59 years old, and are located in the region of Mlati, Sleman, Yogyakarta, Indonesia. A random sample of the study was conducted using simple random sampling with SPSS 22 software. There were 143 samples that conform to the inclusion criteria of prehypertension, high normal uric acid (≥ 5 to < 7 mg/dL), negative urine protein, and negative urine reduction. Exclusion criteria included a history of diabetes, chronic renal failure, use of hormonal contraception, pregnancy, hypertension, ages < 30 or > 59 years old, the consumption of uric-acid-lowering drugs (allopurinol, probenecid), uric acid levels < 5 mg/dL or ≥ 7 mg/dL, creatinine levels > 1.5 g/dL, and fasting blood glucose (FBG) > 126 g/dL. From 143 samples randomized to two groups, group I was given 2x100 g/day of soursop supplement and group II was without soursop. Laboratory examinations of serum potassium, total cholesterol, LDL, HDL, and triglycerides were performed at weeks 0, 7, and 13 in the soursop and non-soursop groups. Compliance with the soursop consumption was evaluated every 2 weeks for 3 months. The study was conducted with RCTs. Data analysis was performed using an independent *t* test, a nonparametric Mann–Whitney test, and a chi-square test.

**RESULTS**

The study involved 143 subjects, such as 71 subjects soursop and 72 subjects non-soursop groups. The 71 subjects soursop group was 15 subjects (21%) are drop out at week 7 and 17 subjects (23%) at week 13. The 72 subjects non-soursop group was 12 subjects are drop out (16%) at week 7 and 14 subjects (19%) at week 13.

TABLE 1. Age and gender in the soursop and non-soursop groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable |  | Soursop | Non-soursop | *p* |
| *n* = 143  Mean (SD) | *n* = 71  Mean (SD) | *n* = 72  Mean (SD) |
| Age  (years) | 45.36  (7.76) | 46.30  (7.95) | 44.44  (7.52) | 0.107\* |
| Gender |  |  |  | 0.268\* |
| Male | 107 (74.8%) | 56 (39.2%) | 51 (35.7%) |
| Female | 36 (25.2%) | 15 (10.5%) | 21 (14.7%) |

Note: \*analysis *t* test, \*\*analysis Mann–Whitney test.

The mean age of the soursop group is 46.30 ± 7.95 years old, and the mean age of the non-soursop group is 44.44 ± 7.52 years old. There was no significant difference between the mean age of the two groups soursop and non-soursop (*p* = 0.107). The gender breakdown in the soursop group is 56 (79%) males and 15 (21%) females, while the number of males in the non-soursop group is 51 (71%) and the number of females is 21 (29%). There was no significant difference between the males and females of the two groups soursop and non-soursop (*p*=0.268, TABLE 1).

TABLE 2. Mean potassium, total cholesterol, LDL, HDL, and triglycerides

at weeks 0, 7, and 13 in the soursop and non-soursop groups.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Week 0 | | | Week 7 | | | Week 13 | | |
| Soursop  *n* = 71  Mean (SD) | Non-soursop  *n* = 72  Mean (SD) | *p* | Soursop  *n* = 56  Mean (SD) | Non-soursop  *n* = 60  Mean (SD) | *p* | Soursop  *n* = 54  Mean (SD) | Non-soursop  *n* = 58  Mean (SD) | *p* |
| **Potassium (mg/dL)** | 3.90  (0.35) | 3.88  (0.32) | 0.905\*\* | 4.09  (0.37) | 3.99  (0.32) | 0.073\* | 4.04  (0.30) | 3.95  (0.36) | 0.108\* |
| **Chol (mg/dL)** | 164.76 (34.20) | 167.81 (34.33) | 0.596\* | 191.59 (27.86) | 187.77 (31.91) | 0.254\* | 182.81 (21.84) | 185.86 (28.26) | 0.932\* |
| **LDL (mg/dL)** | 108.51  (26.74) | 109.04 (30.78) | 0.912\* | 127.57 (21.72) | 121.67 (28.57) | 0.221\* | 124.33 (18.92) | 121.95 (27.21) | 0.710\* |
| **HDL (mg/dL)** | 41.54 (10.11) | 42.85 (10.54) | 0.449\* | 44.18 (9.28) | 44.30 (11.85) | 0.400\* | 45.30 (10.03) | 47.12 (13.00) | 0.960\* |
| **Trigly (mg/dL)** | 118.54 (69.25) | 124.47 (74.55) | 0.634\*\* | 147.54 (86.42) | 168.32 (198.05) | 0.423\*\* | 138.81 (60.82) | 164.66 (168.12) | 0.580\*\* |

Note: \*analysis *t* test, \*\*analysis Mann–Whitney test.

The mean potassium level at baseline (week 0) of the soursop group was 3.90 ± 0.35 mg/dL, and for the non-soursop group it was 3.88 ± 0.32 mg/dL. There was no significant difference in the baseline potassium levels in the two groups (*p*=0.905). At week 7, the potassium level of the soursop group was 4.09 ± 0.37 mg/dL, and in the non-soursop group it was 3.99 ± 0.32 mg/dL. There was no significant difference in the two groups (*p*=0.073). At week 13, the soursop group level was 4.04 ± 0.30 mg/dL, and the non-soursop group level was 3.95 ± 0.36 mg/dL. There was no significant difference in the two groups (*p*=0.108; TABLE 2).

The mean total cholesterol level at baseline (week 0) of the soursop group was 164.76 ± 34.20 mg/dL, and it was 167.81 ± 34.33 mg/dL in the non-soursop group. There was no significant difference in the baseline total cholesterol levels in the two groups (*p*=0.596). At week 7, the soursop group level was 191.59 ± 27.86 mg/dL, and the non-soursop group level was 187.77 ± 31.91 mg/dL. There was no significant difference in the two groups (*p* = 0.254). At week 13, the soursop group level was 182.81 ± 21.84 mg/dL, and the non-soursop group level was 185.86 ± 28.26 mg/dL. There was no significant difference in the two groups (*p* = 0.932; TABLE 2).

The mean LDL level at baseline (week 0) of the soursop group was 108.51 ± 26.74 mg/dL, and the for the non-soursop group it was 109.04 ± 30.78 mg/dL. There was no significant difference in baseline LDL levels in the two groups (*p* = 0.912). At week 7, the soursop group level was 127.57 ± 21.72 mg/dL, and in the non-soursop group it was 121.67 ± 28.57 mg/dL. There was no significant difference in the two groups (*p* = 0.221). At week 13, the soursop group level was 124.33 ± 18.92 mg/dL, and the non-soursop group level was 121.95 ± 27.21 mg/dL. There was no significant difference in the two groups (*p* = 0.710; TABLE 2).

The mean HDL level at baseline (week 0) of the soursop group was 41.54 ± 10.11 mg/dL, and in the non-soursop group it was 42.85 ± 10.54 mg/dL. There was no significant difference in the baseline HDL levels in the two groups (*p*=0.449). At week 7, the soursop group level was 44.18 ± 9.28 mg/dL, and the non-soursop group level was 44.30 ± 11.85 mg/dL. There was no significant difference in the two groups (*p*=0.400). At week 13, the soursop group level was 45.30 ± 10.03 mg/dL, and the non-soursop group level was 47.12 ± 13.00 mg/dL. There was no significant difference in the two groups (*p*=0.960; TABLE 2).

The mean triglyceride level at baseline (week 0) of the soursop group was 118.54 ± 69.25 mg/dL, and in the non-soursop group it was 124.47 ± 74.55 mg/dL. There was no significant difference in baseline triglyceride levels in the two groups (*p*=0.634). At week 7, the soursop group level was 147.54 ± 86.42 mg/dL, and the non-soursop group level was 168.32 ± 198.05 mg/dL. There was no significant difference in the two groups (*p*=0.423). At week 13, the soursop group level was 138.81 ± 60.82 mg/dL, and the non-soursop group level was 164.66 ± 168.12 mg/dL. There was no significant difference in the two groups (*p*=0.580; TABLE 2).

**DISCUSSION**

The recommended intake of potassium in a standard diet is 4.7 g/day (120 mmol/day); for mild to moderate chronic kidney disease it is < 4.7 g/day, and in severe chronic kidney disease (including those undergoing dialysis) it is < 3 g/day (TABLE 3).7 Those with low-potassium diets are at risk for cardiac arrhythmias and constipation.

TABLE 3. Recommended dietary potassium intake in normal and chronic kidney disease

|  |  |  |  |
| --- | --- | --- | --- |
|  | Normal | Mild to moderate CKD | Severe dialysis CKD |
| Potassium (g/day) | 4.7  (120 mmol/day) | < 4.7  (< 120 mmol/day) | < 3  (< 77 mmol/day) |

At week 7, the mean potassium levels of the soursop group increased from 3.90 ± 0.35 to 4.09 ± 0.37 mg/dL, but in the non-soursop group there was also an increase from 3.88 ± 0.32 to 3.99 ± 0.32 mg/dL. In the statistical analysis, there was no significant difference between the soursop and non-soursop groups (*p*=0.073). At week 13, the mean potassium levels of the soursop group increased from 3.90 ± 0.35 to 4.04 ± 0.30 mg/dL, but in the non-soursop group there was also an increase from 3.88 ± 0.32 to 3.95 ± 0.36 mg/dL. In the statistical analysis, there was no significant difference between the soursop and non-soursop groups (*p*=0.108). This study indicate soursop consumption 2x100 g/day for 3 months there was no significant difference in serum potassium levels between the soursop and non-soursop groups. Soursop consumption of 2x100 g/day is equivalent to 556 mg/day of potassium; this is well below the recommended dietary intake for mild to severe chronic kidney disease, even for those undergoing dialysis (Table 3). This means that the consumption of soursop fruit for patients with mild to severe chronic kidney disease (dialysis) is still safe.

Several studies have suggested that soursop consumption is beneficial for kidney disease.3 Surveys-based studies have been conducted in various places including Peru4 and Bolivia5 on the use of soursop in the traditional treatment of kidney disease. Sja'bani (2014) in his report the consumption of 2x100 g/day soursop juice in patients with chronic kidney disease in Yogyakarta, Indonesia can decrease uric acid, serum ureum and creatinine, without causing negative effects.6

In a review journal of the NKF (National Kidney Foundation), the issue of whether a high-potassium diet restriction can prevent hyperkalemia in patients undergoing hemodialysis was explored. After study and data collection, it was found that a high-potassium diet restriction was required to prevent hyperkalemia in patients undergoing hemodialysis.16

Patients with chronic kidney disease tend to have hyperkalemia.17 They worry about the consumption of fruit for fear of increased serum potassium levels and therefore require a restricted potassium diet. Soursop fruit is beneficial for chronic kidney disease,6 and in this study the consumption of soursop was found to have no significant effect on potassium levels compared to the group without soursop. So the consumption of soursop on chronic kidney disease is safe because it does not cause hyperkalemia and is beneficial because several other studies have stated about the benefits of soursop on kidney disease.

This cardiovascular risk study aims to examine the effect of the consumption of 2 x 100 g/day of soursop supplement on cardiovascular risk (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). Soursop fruit contains tannins,14 which play a role in the reduction of triglycerides.15 Soursop fruit also contains flavonoids,13 which can inhibit the activity of the HMG-CoA reductase enzyme in the cholesterol synthesis process. The inhibition of this enzyme activity results in the absence of mevalonate from HMG-CoA; mevalonate will be converted to squalene, lanosterol, dihydrolanosterol, D 8-dimethylsterol, 7-dihydrocholesterol, and eventually cholesterol. In addition, flavonoids also have a positive effect in decreasing total cholesterol levels through the increased excretion of bile acids with feces. Tannins, riboflavin, and cyanide acid have a hypoglycemic effect that can lower cholesterol and triglyceride blood levels in mice.15,18

Flavonoids in soursop leaves and fruit are antioxidants that have the ability to reduce fat emulsion and cholesterol synthesis. Decreasing fat emulsions and cholesterol synthesis will lower the levels in the blood.18 Soursop fruit also contains many antioxidants.13 Most fruit is rich in antioxidant compounds that can prevent and inhibit damage from fats, proteins, and nucleic acids.19 The abundant antioxidants in fruit are polyphenols and vitamins (A, B, C, E) including flavonoids.20

The consumption of a soursop fruit supplement of 2x100 g/day for 3 months led to no significant difference in total cholesterol at week 7 (*p*=0.254) and week 13 (*p*=0.932) between the soursop and non-soursop groups. For LDL cholesterol there was no significant difference at week 7 (*p*=0.221) and week 13 (*p*=0.710). For HDL cholesterol there was no significant difference at week 7 (*p*=0.400) and week 13 (*p*=0.960). There was no difference in triglyceride levels at week 7 (*p*=0.423) and week 13 (*p*=0.580) between the soursop and non-soursop groups.

No similar research has been conducted on the effect of soursop consumption on cardiovascular risk in humans, only in animals. Firmansyah et al. (2016), who administered soursop leaf extract to hyperglycemic rats, found that it did not lower total cholesterol and triglycerides significantly, but it decreased the blood sugar of mice.21 However, the administration of soursop leaf extract with ethyl acetate solvent can significantly decrease total blood cholesterol levels in mice.22 Likewise, Posangi et al. (2012) concluded that administering soursop leaf extract can reduce total cholesterol in mice.23

Pratiwi et al. (2017) found that the essential oil of soursop leaves (*Annona muricata* Linn.) contains terpenoid, alkaloid, and phenolic compounds. Terpenoids, alkaloids, and phenolics serve as antioxidants and anti-inflammatories in the right dosage. If the dose is high and administered for a long time, the terpenoids, alkaloids, and phenolics will become toxic and result in increased LDL and decreased HDL. A dosage of soursop leaf oil of 2.5 mg/kg W is a safe dose that does not increase LDL levels and decreases subchronic HDL levels in normal male and female rats.24

Tia et al. (2014) reported the percentages of decrease in the LDL cholesterol serum levels of white rats from various dosages of soursop juice: a dose of 0.9 g/200 g W is equal to 46.19%, a dose of 1.8 g/200 g W is equal to 52.30%, and a dose of 2.7 g/200 g W is equal to 61.62%. There is an effect of administering various doses of soursop juice on the decrease in LDL cholesterol serum levels in white mouse dyslipidemia. The greater the dose of soursop juice, the greater the decrease in LDL cholesterol levels in the serum of white rats with dyslipidemia.25

de la Cruz (2016) concluded that dried soursop fruit significantly lowers cholesterol, triglycerides, and LDL cholesterol in hyperlipidemic rats. The dosages of soursop fruit used were 500, 1000, 2000 mg/kg W. The higher the dose, the greater the decrease in cholesterol, triglyceride levels, and LDL levels.26 Syahida et al. (2012) showed that the higher the provision of soursop extract given to rats, the higher the level of antioxidants.27 Yuliantari et al. (2017) researched the influence of temperature and extraction on the flavonoid content and antioxidant activity of soursop leaves. They showed that the best result is at a temperature of 45°C and a time of extraction of 20 minutes. The total yield is 19.14% flavonoid 903.90 mgQE/g extract material, and the lowest antioxidant activity is 258.155 mg/L.28

Tugiyanti et al. (2016) showed that a soursop leaf supplement in male ducks of 8.36% showed the highest HDL level of 99.89 mg/dL. However, a soursop flour supplement up to 15% had not been able to reduce triglycerides, cholesterol, and LDL blood levels in male ducks aged 10 weeks. Soursop leaves have antioxidant flavonoid content. Tugiyanti et al. (2016) states that antioxidants can affect fat content.18 Wulandari et al. (2015) concluded that soursop leaf extract with ethanol solvent can lower triglyceride levels and increase HDL levels in male wistar rats.29

How does this study compare with other research on the effect of soursop on cardiovascular risk? TABLE 4 explains briefly.

TABLE 4. Comparison of this study with other soursop research on cardiovascular risk.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Haidar, 2018 | Tia, 2014 | Tugiyanti et al., 2016 | de la Cruz, 2016 |
| Material | Soursop fruit juice | Soursop fruit juice | Soursop leaf flour | Dried soursop fruit |
| Subject | Healthy human | Dyslipidemia mice | Healthy ducks | Dyslipidemia mice |
| Given by | Oral | Oral | Oral | Oral |
| Dose | 2 x 100 g/day | 0.9 g/200 g W  1.8 g/200 g W  2.7 g/200 g W | Fodder + 5%; 10%; 15% Soursop leaf flour | 500 mg/kg W  1000 mg/kg W  2000 mg/kg W |
| Method | Cohort, 3 months, RCT | Control group design | Completely randomized design, 5 weeks | Completely randomized design, 30 days |
| Evaluation | Every 2 weeks | Pre- and post-test | Pre- and post-test | Pre- and post-test |
| Result | No significant effect on the decrease in total cholesterol, LDL, or triglycerides and an increase in HDL at week 7 and 13in the soursop and non-soursop groups. | There is the effect of giving various doses of soursop juice on the decrease in LDL cholesterol levels. The greater the dose, the greater the decrease in LDL cholesterol levels. | Cannot lower triglycerides, cholesterol, and blood LDL and triglyceride levels. | Significantly lower cholesterol, triglycerides, and LDL. The higher the dose, the greater the decrease. |

In a study on dyslipidemia in mice, Tia (2014) found that soursop juice can lower LDL. Research by de la Cruz (2016) on dyslipidemia in mice concluded that soursop can lower cholesterol, triglycerides, and LDL. Haidar (2018) found that soursop juice in healthy humans had no significant effect in decreasing cholesterol, LDL, or triglycerides, and HDL increased in the 7th and 13th weeks for the soursop and non-soursop groups. Why is there no significant difference in total cholesterol, LDL, HDL, or triglycerides among the soursop and non-soursop groups at weeks 7 and 13? We suspect that the subjects of the study were healthy subjects rather than subjects with cardiovascular disorders (dyslipidemia) as in other studies. When the subjects who initially had dyslipidemia (hypercholesterolemia, high LDL, low HDL, and hypertriglyceridemia) are compared to the soursop and non-soursop groups, the results are as follows:

TABLE 5. Subject dyslipidemia in the soursop and non-soursop groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Hypercholesterol | Week 0  (*n* = 22) | | Week 7  (*n* = 17) | | Week 13  (*n* = 17) | |
| Soursop  (*n* = 10) | Non-soursop  (*n* = 12) | Soursop  (*n* = 7) | Non-soursop  (*n* = 10) | Soursop  (*n* = 7) | Non-soursop  (*n* = 10) |
| 221.30  SD 17.30 mg/dL | 223.25  SD 15.88 mg/dL | 213.57  SD 19.67 mg/dL | 223.70  SD 25.06 mg/dL | 197.57  SD 33.64 mg/dL | 220.70  SD 18.06 mg/dL |
| High LDL | Week 0  (*n* = 81) | | Week 7  (*n* = 63) | | Week 13  (*n* = 61) | |
| Soursop  (*n* = 42) | Non-soursop  (*n* = 39) | Soursop  (*n* = 33) | Non-soursop  (*n* = 30) | Soursop  (*n* = 32) | Non-soursop  (*n* = 29) |
| 126.86  SD 16.75 mg/dL | 131.69  SD 21.53 mg/dL | 135.73  SD 20.44 mg/dL | 137.07  SD 24.38 mg/dL | 130.53  SD 18.20 mg/dL | 134.24  SD 26.61 mg/dL |
| Low HDL | Week 0  (*n* = 60) | | Week 7  (*n* = 49) | | Week 13  (*n* = 46) | |
| Soursop  (*n* = 32) | Non-soursop  (*n* = 28) | Soursop  (*n* = 26) | Non-soursop  (*n* = 23) | Soursop  (*n* = 25) | Non-soursop  (*n* = 21) |
| 32.50  SD 5.00  mg/dL | 32.54  SD 4.69  mg/dL | 40.15  SD 8.63 mg/dL | 40.61  SD 10.57 mg/dL | 41.12  SD 7.73 mg/dL | 42.19  SD 13.43 mg/dL |
| Hypertriglyceride | Week 0  (*n* = 35) | | Week 7  (*n* = 29) | | Week 13  (*n* = 28) | |
| Soursop  (*n* = 18) | Non-soursop  (*n* = 17) | Soursop  (*n* = 14) | Non-soursop  (*n* = 15) | Soursop  (*n* = 14) | Non-soursop  (*n* = 14) |
| 205.28  SD 83.52 mg/dL | 233.47  SD 77.80 mg/dL | 183.07  SD 90.76 mg/dL | 339.67  SD 342.53 mg/dL | 188.29  SD 64.51 mg/dL | 324.21  SD 276.16 mg/dL |

There were 22 subjects with hypercholesterolemia at week 0 and 17 at weeks 7 and 13. The mean value for subjects with hypercholesterolemia who consumed soursop at week 7 showed decreased cholesterol averages from 221 mg/dL to 213 mg/dL. At week 13, the average value for cholesterol decreased from 221 mg/dL to 197 mg/dL when compared with week 0. From week 7 to week 13, the average cholesterol value decreased from 213 mg/dL to 197 mg/dL. Regarding the mean value for subjects with hypercholesterolemia without soursop consumption, at week 7 cholesterol did not decrease (it stayed at 223 mg/dL). At week 13, the value of the cholesterol average decreased from 223 mg/dL to 220 mg/dL when compared with week 0. Without soursop consumption in subjects with hypercholesterolemia, there was almost no change for 13 weeks. From this study, it can be concluded that the consumption of soursop fruit in subjects with hypercholesterolemia can reduce cholesterol averages at weeks 7 and 13 compared to the group without the consumption of soursop.

There were 81 subjects with high LDL at week 0, 63 subjects at week 7, and 61 subjects at week 13. The mean value for high LDL subjects in the soursop consumption group at week 7 increased from 126 mg/dL to 135 mg/dL and at week 13 from 126 mg/dL to 130 mg/dL. Regarding the mean values for high LDL subjects without soursop, at week 7 the average LDL increased from 131 mg/dL to 137 mg/dL. At week 13, the mean LDL value increased from 131 mg/dL to 134 mg/dL when compared with week 0. From this research, it can be concluded that the consumption of soursop fruit in subjects with high LDL did not lower mean LDL at weeks 7 and 13 compared to the group without the consumption of soursop.

There were 60 subjects with low HDL at week 0, 49 subjects at week 7, and 46 subjects at week 13. The mean value for low HDL subjects with soursop consumption increased at week 7 and week 13 from 32 to 40 and 41 mg/dL, respectively. Regarding the mean value for low HDL subjects without soursop consumption, at weeks 7 and 13 it increased from 32 to 40 and 42 mg/dL, respectively. From this research it can be concluded that the consumption of soursop fruit does not increase mean HDL cholesterol compared to the non-soursop group.

There were 35 subjects with hypertriglyceridemia at week 0, 29 subjects at week 7, and 28 subjects at week 13. The mean value for hypertriglyceridemia subjects with the consumption of soursop decreased from 205 to 183 mg/dL and 188 mg/dL, respectively, at weeks 7 and 13. Regarding the mean value for hypertriglyceridemia subjects without soursop consumption, at weeks 7 and 13 it increased from 233 to 339 mg/dL and 324 mg/dL, respectively. From this research it can be concluded that the consumption of soursop fruit can lower mean triglyceride levels compared to the group without soursop consumption.

**CONCLUSION**

Serum potassium levels did not differ significantly between groups with the consumption of a soursop supplement of 2x100 g/day and without soursop at week 7 (*p*=0.073) and week 13(*p*=0.108). The potassium content in 2x100 g/day of soursop fruit is equivalent to 556 mg/day; this is well below the recommended dietary intake for mild to severe chronic kidney disease, even for those undergoing dialysis. Soursop consumption is safe and useful in patients with mild to severe chronic kidney disease. The consumption of a soursop fruit supplement did not differ significantly in improving cardiovascular risk (decreased total cholesterol, LDL, and triglycerides and increased HDL). But in subjects with hypercholesterolemia and hypertriglyceridemia, the consumption of soursop decreased average cholesterol and triglyceride levels at weeks 7 and 13 compared to no soursop consumption.

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**REFERENCE**

1. Çorbacıoğlu ŞK, Güler S, Yağmur D, Ülker V, Kılıçaslan İ. Aşırı Miktarda Kayısı ve Muz Tüketimi Sonrası Ciddi Hiperkalemi: İki Olgu Sunumu ve Literatürün Gözden Geçirilmesi. *Turk J Emerg Med*. 2012;12(1):041-044. doi:10.5505/1304.7361.2012.38278.

2. Pavletic AJ. Hyperkalemia Induced by Excessive Consumption of Dried Fruits-Manifestation of an Undiagnosed Eating Disorder? *Psychosomatics*. 2011;52(5):494-495. doi:10.1016/j.psym.2011.01.011.

3. Badrie N, Schauss AG. Soursop (Annona muricata L.): composition, nutritional value, medicinal use, and toxicology. In: *Bioactive Foods in Promoting Health, Fruit and Vegetables*. Oxford: Academic Press; 2010:621-643. doi:10.1016/B978-0-12-374628-3.00039-6.

4. Monigatti M, Bussmann RW, Weckerle CS. Medicinal plant use in two Andean communities located at different altitudes in the Bolívar Province, Peru. *J Ethnopharmacol*. 2013;145(2):450-464. doi:10.1016/j.jep.2012.10.066.

5. Hajdu Z, Hohmann J. An ethnopharmacological survey of the traditional medicine utilized in the community of Porvenir, Bajo Paraguá Indian Reservation, Bolivia. *J Ethnopharmacol*. 2012;139(3):838-857. doi:10.1016/j.jep.2011.12.029.

6. Sja’bani M, Irijanto F, Prasanto H, et al. Soursop Consumption Supplement In Pre And Stage 1 Hypertension Kidney Disease Patients With Hyperuricemia. *Nephrology*. 2014;19(S2):77-202 PS3-082. https://onlinelibrary.wiley.com/doi/full/10.1111/nep.12237. Accessed March 20, 2018.

7. Kalantar-Zadeh K, Fouque D. Nutritional Management of Chronic Kidney Disease. *N Engl J Med*. 2017;377(18):1765-1776. doi:10.1056/NEJMra1700312.

8. WHO | World Heart Day 2017. http://www.who.int/cardiovascular\_diseases/world-heart-day-2017/en/. Accessed April 23, 2018.

9. Sutters M. Systemic Hypertension. In: Papadakis MA, McPhee SJ, Rabow MW, eds. *Current Medical Diagnosis & Treatment 2017*. New York, NY: McGraw-Hill Education; 2017. accessmedicine.mhmedical.com/content.aspx?aid=1132697554. Accessed November 8, 2017.

10. Ishikawa Y, Ishikawa J, Ishikawa S, et al. Prehypertension and the risk for cardiovascular disease in the Japanese general population: the Jichi Medical School Cohort Study. *J Hypertens*. 2010;28(8):1630-1637. doi:10.1097/HJH.0b013e32833a8b9f.

11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. January 2017:HYP.0000000000000065. doi:10.1161/HYP.0000000000000065.

12. Gavamukulya Y, Wamunyokoli F, El-Shemy HA. Annona muricata: Is the natural therapy to most disease conditions including cancer growing in our backyard? A systematic review of its research history and future prospects. *Asian Pac J Trop Med*. 2017:1-14. doi:10.1016/j.apjtm.2017.08.009.

13. Coria-Téllez AV, Montalvo-Gónzalez E, Yahia EM, Obledo-Vázquez EN. Annona muricata: A comprehensive review on its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity. *Arab J Chem*. 2016. doi:10.1016/j.arabjc.2016.01.004.

14. Onyechi AU, Ibeanu VN, Eme PE, Kelechi M. Nutrient, Phytochemical Composition and Consumption Pattern of Soursop (Annona muricata) Pulp and Drink among Workers in University of Nigeria, Nsukka Community. *Pak J Nutr*. 2015;14(12):866-870. doi:10.3923/pjn.2015.866.870.

15. Wurdianing I, Nugraheni SA, Rahfiludin Z. Efek ekstrak daun sirsak (Annona muricata Linn) terhadap profil lipid tikus putih jantan (Rattus Norvegicus). *J GIZI Indones*. 2014;3(1):7-12. doi:10.14710/jgi.3.1.96-101.

16. St-Jules DE, Goldfarb DS, Sevick MA. Nutrient Non-equivalence: Does Restricting High-Potassium Plant Foods Help to Prevent Hyperkalemia in Hemodialysis Patients? *J Ren Nutr*. 2016;26(5):282-287. doi:10.1053/j.jrn.2016.02.005.

17. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med*. 2009;169(12):1156-1162. doi:10.1001/archinternmed.2009.132.

18. Tugiyanti E, Heriyanto S, Syamsi AN. Pengaruh Tepung Daun Sirsak (Announa Muricata L) terhadap Karakteristik Lemak Darah dan Daging Itik Tegal Jantan. *Bul Peternak*. 2016;40(3):211. doi:10.21059/buletinpeternak.v40i3.11243.

19. Shi HL, Noguchi N, Niki E. Introducing natural antioxidants. In: Pokorný J, Yanishlieva N, Gordon M, eds. *Antioxidants in Food: Practical Applications*. 1st Edition. Cambridge: Woodhead Publishing; 2001.

20. Fleuriet A, Macheix JJ. Phenolic acids in fruits and vegetables. In: Rice-Evans CA, Packer L, eds. *Flavonoids in Health and Disease*. 2nd Edition. New York: CRC Press; 2003.

21. Firmansyah D, Bachri MS, Nurkhasanah N. Pengaruh Pemberian Ekstrak Etanol Dan Kloroform Daun Sirsak Terhadap Kolesterol Total Dan Trigliserida Pada Tikus Yang Diinduksi Aloksan. *Pharmaciana*. 2016;6(1). http://journal.uad.ac.id/index.php/pharmaciana/article/view/3221. Accessed September 16, 2017.

22. Tobat SR. Uji efektifitas ekstrak daun sirsak (Annona Muricata l.) Dengan Menggunakan Beberapa Jenis Pelarut Terhadap Kadar Kolesterol Total Darah Mencit Putih Jantan. *Indones Nat Res Pharm J*. 2017;1(2). http://journal.uta45jakarta.ac.id/index.php/inrpj/article/view/800. Accessed October 10, 2017.

23. Posangi I, Posangi J, Wuisan J. Efek ekstrak daun sirsak (Annona Muricata l.) pada kadar kolesterol total tikus wistar. *J Biomedik*. 2012;4(1). https://ejournal.unsrat.ac.id/index.php/biomedik/article/view/750. Accessed October 10, 2017.

24. Pratiwi YI, Purwanti S, Damayanti DS. Pengaruh Pemberian secara Subkronik Minyak Atsiri Daun Sirsak (Annona muricata Linn.) terhadap Kadar Low Density Lipoprotein (LDL) dan High Density Lipoprotein (HDL) Serum Tikus Wistar. *JIMR - J Islam Med Res*. 2017;1(1). http://riset.unisma.ac.id/index.php/fk/article/view/491. Accessed October 10, 2017.

25. Tia HD, Sistiyono S, Hendarta NY. Pengaruh Berbagai Dosis Jus Buah Sirsak (Annona muricata L.) Terhadap Penurunan Kadar Kolesterol Low Density Lipoprotein (LDL) Serum Tikus Putih (Rattus norvegicus) Dislipidemia. *J Teknol Lab*. 2014;3(2):84-90. http://www.teknolabjournal.com/index.php/Jtl/article/view/65. Accessed October 8, 2017.

26. de la Cruz AMA, Catabay AP. Hypolipidemic Effect of the Lyophilized Fruit Pulp of Guyabano, Annona Muricata Linn. (Fam. Annonaceae) in Atherogenic Diet-Induced Hyperlipidemia in Albino Rats. *JAASP*. 2016;1:351-359. http://www.aaspjournal.org/abstractinfo.php?id=74. Accessed October 10, 2017.

27. Syahida M, Maskat MY, Suri R, Mamot S, Hadijah H. Soursop (Anona muricata L.): Blood hematology and serum biochemistry of sprague-dawley rats. *Int Food Res J*. 2012;19(3):955-959. https://ukm.pure.elsevier.com/en/publications/soursop-anona-muricata-l-blood-hematology-and-serum-biochemistry-. Accessed October 9, 2017.

28. Yuliantari NWA, Widarta IWR, Permana IDGM. Pengaruh Suhu dan Waktu Ekstraksi Terhadap Kandungan Flavonoid dan Aktivitas Antioksidan Daun Sirsak (Annona muricata L.) Menggunakan Ultrasonik. *Media Ilm Teknol Pangan*. 2017;4(1):35-42. https://doaj.org. Accessed October 9, 2017.

29. Wulandari RL, Susilowati S, Amelya S. Pengaruh Kombinasi Ekstrak Etanol Daun Sirsak Dan Gemfibrozil Terhadap Kadar Trigliserida Dan HDL Tikus Yang Diinduksi Pakan Tinggi Lemak. *E-Publ Fak Farm*. 2015;0(0):78-84. https://publikasiilmiah.unwahas.ac.id/index.php/Farmasi/article/view/1348. Accessed October 10, 2017.