Grape Seed Effects on Blood Pressure and Plasma Lipid Level

Daniela Angeline,[1] Michelle Martina[2]

[1]General Practitioner in Ade Mohammad Djoen General Hospital, Sintang, West Borneo

[2]General Practitioner in North Jakarta, Indonesia

ABSTRACT

Grape seed is known for its antioxidative and anti-inflammatory properties. This paper discuss its benefits on human, such as reducing blood pressure and plasma lipid level, therefore reducing atherosclerosis risk and subsequently prevent cardiovascular diseases.

Keywords: Blood pressure, grape seed, hypertension, plant-derived therapeutics, plasma lipid

ABSTRAK

Biji anggur dikenal karena efek antioksidatif dan anti-inflamasi. Tulisan ini bertujuan untuk menjelaskan komponen dalam biji anggur dan manfaatnya bagi manusia, seperti efek menurunkan tekanan darah dan kadar lipid plasma, sehingga dapat mengurangi risiko aterosklerosis dan dapat mencegah penyakit kardiovaskuler. **Daniela Angeline, Michelle Martina. Efek Biji Anggur terhadap Tekanan Darah dan Kadar Lipid Plasma**

Kata kunci: Biji anggur, hipertensi, lipid plasma, tekanan darah, terapi dari tumbuhan

BACKGROUND

Cardiovascular diseases (CVDs) is one of the leading cause of deaths worldwide, causing approximately 17.9 million deaths in 2016, or 31% of all deaths globaally.[1] Eighty-five percents of these CVDs deaths are due to heart attack and stroke.[1] Most deaths occured in low- and middle-income countries as people are not provided with early detection nor treatment for risk factors.[1] To reduce high level of circulating lipids and reduce blood pressure, most physicians will prescribe HMG-CoA reductase inhibitors and anti-hypertensive drugs. Various pharmaceutical companies offer different approaches from conventional drugs to plant-derived therapeutics. One of these known plants-derived therapeutics is grape seed extract. Several in vitro and animal studies showed that compounds in grape seed have positive effects in modulating different factors associated to CVDs. This paper reviews the human studies of grape seed extract.

Grape Seed Component and Benefits

Sativa grapes *(Vitis vinifera L)* has been worldwide's interest due to its nutritional benefits for human health. Different components in the grapes have benefits for health, such as grape seed extract and also grape skin. Grape seed extract contain high concentration of polyphenols, mostly monomeric flavan-3-ols and oligomeric proanthocyanidins.[2] Grape seed has high antioxidant properties which work by modulating antioxidant enzyme expression, therefore lowering the oxidative damage in cells, works as anti-inflammatory and anti-atherosclerotic agent.[3] Due to its anti-atherosclerotic effect, grape seed extract has cardioprotective effect to the heart by modulating different risk factor contributing to CVDs such as hypertension and dyslipidemia. Other proven health benefit antimicrobial and anticancer properties.[4]

Grape seeds contain protein (11%), fiber (35%), minerals (3%), water (7%), and 7 to 20% lipid content.[5] Factors influencing the constituent of the grape seed includes the type of grape, ripeness, geographic environment, climate condition. Different microbiota in different individual and genetic profile also differs the bioavailability of grape seed extract.[6] The two most common components produced are grape seed extract and grape seed oil according to their manufacturing process.

Grape seed has polyphenol compound which are mainly flavonoids, monomeric phenolic compounds such as catechins, epicatechins and epicatechin-3-O-gallate and dimeric, trimeric and tetrameric procyanidins.[5] The 90% of main polyphenols identified in grape seed are procyanidins which are the most interesting constituent found in grape seed and 7% other polyphenol compounds.[3] As this constituent are very beneficial, researchers began to search for the main source of procyanidins in grape, and found that one of the most concentrated part are inside the seed of grape.[6]

Grape seed oil content usually derived from mechanical extraction or organic solvent. The oil content of grape seeds are linoleic acid which belong to the group of polyunsaturated fatty acid (PUFA) that has been proven to have a good effect of human health.[7] The grape seed has PUFA ranging from 85%-90% and also have oleic acid which belong to the group

Alamat Korespondensi *email: dnl.angie@gmail.com*


monounsaturated fatty acid (MUFA) in lower quantity.[7] Grape seed also have high content of vitamin E. Grape variety and environmental cultivation conditions differs the fatty acid composition and vitamin E content.[7]

The constituent of grape seed have a broad range of health benefits. The beneficial effect of grape seed to minimize the risk factor of CVDs derived from its antioxidative and anti-inflammatory properties which can help to eliminate free radicals and prevent lipid oxidation and hence will decrease LDL level and reducing atherosclerosis. In a study conducted by Cao,[8] 287 patients with asymptomatic atherosclerotic plaque were given 200 mg grape seed daily for 24 months; the carotid intima-media thickness and carotid plaque was reduced compared to control and therefore significantly lower CVDs events. Other mechanism in which grape seed have cholesterol-lowering effect is by altering the lipid metabolism process.[9] Its ability to inhibit the pancreatic cholesterol esterase even has been proven.[9] Although weaker than simvastatin, it can bind to the bile acids so increases fecal cholesterol excretion and delay cholesterol absorption by reducing solubility of cholesterol in micelles.[9]

High blood pressure has been one of the risk factor regarding CVDs. Another beneficial effect of grape seed is to lower the blood pressure, although it is still debated; a meta-analysis of 9 randomized control trials (RCT) including total 298 samples showed that systolic blood pressure and heart rate was significantly decreased though it is much less than the effect of antihypertensive drugs.[10] Procyanidins in grape seed directly inhibit angiotensin-converting enzymes (ACE) and increase nitric oxide production which helps lowering blood pressure and promotes relaxation and dilation of blood vessels.[6]

Grape Seed Effects on Blood Pressure and Plasma Lipid Level

Earlier in 2004, Clifton, *et al*,[11] showed that grape seed extract could produce 1.1% greater vasodilatation and weak effect of lowering systolic blood presure compared to controls, but no difference were found on lipid level, C-reactive protein (CRP), nitrate and fibrinolytic - factors contributing to endothelial inflammation and atherosclerotic process. Later in 2018, Kim, *et al*,[12] found that a single dose of grape seed reduces BP (systolic, diastolic, and mean arterial pressure/MAP) at rest and during submaximal exercise. Alteration of blood pressure are minimum around 3–4 mmHg reduction in MAP. In prehypertensive males in high metabolic situation, a single dose of grape seed (300 mg) reduces blood pressure, peripheral vasoconstriction, and heart's workload. The hypothesis in this study is that grape seed enhances O_2 delivery by endothelium-dependent vasodilation mechanism, as it increase flow – mediated dilation.[12] Unfortunately this study has small study sample (n=9).

Compared to study by Kim, *et al*,[12], Park, *et al*, in 2016 showed that chronic supplementation (6 weeks) of grape seed (300 mg) also brought similar blood pressure reducing effect, specifically in systolic blood pressure, improved fasting insulin and insulin sensitivity, but no difference in fasting plasma lipids, vascular adhesion molecules, nor endothelial function (measured by flow – mediated dilation/FMD).[13] Another study by Barona, *et al*,[14] showed that grape seed generated lower systolic blood pressure (SBP) and higher FMD responses after 30-days treatment using freeze-dried grape polyphenolic powder in men with metabolic syndrome. The considered difference of grape seed effect on lowering blood pressure is that Barona, *et al*, used higher total phenolic compound (528 mg/day) compared to study by Kim, *et al*, (126 mg/day).[12,14] But no lipid-lowering effect found in these studies.

But Ras, *et al*,[15] showed no significant changes in both systolic and diastolic blood pressure after consuming 300 mg of grape seed for 8 weeks in pre hypertension and grade I hypertension, the slight effect on lowering both systolic and diastolic blood pressure failed to achieve statistically significant result.

Lipid-lowering effect of grape seed is still searched, mostly proven in *in vitro* and animal studies. Studies of grape seed effect on human's plasma lipid level are still lacking. Sano, *et al*,[16] in 2008 has showed that 200 mg and 400 mg of grape seed consumption for 6 weeks and 12 weeks could reduce oxidized-LDL but not to the other plasma lipid level. The plasma total cholesterol was increased but not statistically significant. Lipid lowering effect was also proven in 52 mildly hyperlipidemic patients aged 21-64 years old with tryglyceride (TG) level of 150-250 mg/dL and total cholesterol of 200-300 mg/dL.[17] In this study, the dose of grape seed extract was 200 mg per day for 8 weeks. Compared to control after 8 weeks, they had significantly reduced level of total cholesterol level, LDL level, and oxidized LDL level.[17] But, TG and HDL level wasn't significantly improved.

Discussion

As CVDs burden growing globally, people with high risk factors were motivated to find better diet and healthier lifestyle. One of the purpose is to reduce plasma lipid profile as one of the atherosclerotic culprit which subsequently cause CVDs. One of the suggested functional food is the lipid – lowering effect of grape seed. This effect is mostly proven in *in vitro* setting and animal studies. Studies by Sano, *et al*,[16] and Razavi, *et al*,[17] showed that grape seed has significantly lowered human plasma lipid level. But this effect was not replicated by Park, *et al*,[13] and Barona, *et al*.[14]

Studies by Razavi, *et al*,[17] Sano, *et al*,[16] and Park, *et al*,[13] include similar group age which are between 21–64 years old, 30–70 years old, and 25–65 years old, respectively. The exclusion criteria of those three were also similar such as having lipid-lowering or antihypertensive drugs, diabetes, hepatic dysfunction, eating other health food, but study by Sano, *et al*,[16] did not mention the exclusion of cigarette smoking even they did mention to include only healthy subjects. Razavi, *et al*,[17] showed that grape seed could reduce total cholesterol, LDL cholesterol, and oxidized-LDL, while study by Sano, *et al*,[16] could only prove its effect on oxidized-LDL, and Park, *et al*,[13] showed no significant changes in plasma lipid level. Razavi, *et al*, Sano, *et al*, and Park, *et al*, recruited 52, 61, and 36 subjects, respectively.[13,16,17] Study sample may contribute to this diffrerent results and larger study sample could reduce the bias.

Many other studies also tried to search grape seed effect on hypertension. Kim, *et al*,[12] and Park, *et al*,[13] showed that grape seed could significantly lower blood presure both in single dose and chronic supplementation, although in study by Park, *et al*,[13] only systolic blood pressure was reduced significantly. But Ras, *et al*,[15] showed only slight not statistically significant effect of grape seed in reducing

blood pressure. In these three studies, other factors that should be considered is sample variations; Park, *et al*,[12] sample was 29 people aged 25–65 years old and Ras, *et al*,[15] has 70 participants aged 35-75 years old, both studies recruited both female and male gender but only menopausal females were included in Ras, *et al*,[15] study. Conversely, Kim, *et al*,[12] include only 9 male younger subjects aged 20–24 years old. These differences might attributed to the different results as advancing age and decreasing level of estrogen in postmenopausal women could be one of unmodifiable risk factors of increased blood pressure.[18]

All of this varying result was summarized by meta-analysis by Feringa, *et al*.[10] This meta-analysis of 9 RCT with total inclusion of 298 samples was to evaluate the effect of grape seed on cardiovascular risk factors including systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, LDL or HDL cholesterol, triglycerides, or CRP in human trial. The 9 RCT included in the study showed different results. Feringa, *et al*,[10] concluded that there is a statistically reduced systolic blood pressure with mean reduction of -1.54 mmHg and this attributed to significantly reduced heart rate, but this reduction is still very modest compared to anti-hypertensive drug. There is no significant grape seed effect on other factors included in the study such as total cholesterol, LDL or HDL cholesterol, triglycerides, or CRP.[10]

The different results of grape seed extract in *in vitro* studies compared to RCT might be caused by the different dose and study period. A higher dose of grape seed extract might be needed to make a significant changes in human; there are still no established potential harmful effect of grape seed in human trial.[10] Other study was suggested to discover grape seed effects as an adjuvant to antihypertensive and antihyperlipidemic therapies to patients with high risk factors such as metabolic syndrome. Also, larger randomized controlled trial of grape seed in human is needed .

Conclusion

Grape seed is beneficial in people with modifiable risk factors of cardiovascular diseases, such as hypertension and high plasma lipid level. Various trial has proven its effect in lowering systolic blood pressure, diastolic blood pressure, mean arterial pressure, and reducing plasma lipid level. Hopefully grape seed could reduce the medication burden in people with multiple co-morbidities, but another bigger study is needed.

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