



ANTIHYPERTENSIVE PROPERTIES OF AN APPLE PEEL - CAN APPLE A DAY KEEP A DOCTOR AWAY?

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ABSTARCT : Apples or otherwise botanically known as *Malus domestica* is said to have originated in the mountains of Central and west Asia. It is one of the earliest and most commonly grown tree. In humans it is consumed in various forms and varieties; also it is eaten as a raw fruit. The purpose of this article is to highlight the antihypertensive property of an apple peel along with numerous health benefits of an apple.

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Hypertension is the leading cause of death in the modern world. Allopathic treatment of hypertension which is currently available is mostly accompanied by one or the other side effects and have to be taken lifelong once started. Therefore, people are now bending to the idea of life style modification and dietary changes as the best way to combat mild and moderate forms of Hypertension. In order to escape the unwanted effects of allopathic drugs, several natural compounds are being researched upon for their antihypertensive properties. Antihypertensive drugs have been classified into several groups depending on their mode of action. One such group of drugs is ACE-inhibitors which is of great interest as far as antihypertensive action of an apple is concerned. Several properties like lowering of blood cholesterol specially LDL, weight loss, antioxidant action and prevention of atherosclerosis have been identified as various blood pressure lowering mechanisms of an apple. It is concluded from this article that the flavonoids such as Quercetin, Proanthocyanidin present in the peel of an apple along with pectin can help in reducing the blood pressure among which inhibition of Angiotensin converting enzyme is one of the important mechanism.

Keywords: Hypertension, apple, flavonoids, quercetin, pectin, ACE inhibitors

INTRODUCTION

Hypertension is said to be better prevented than cure. It is because of the fact that the treatment of hypertension is incomplete unless associated with certain lifestyle changes and dietary modifications. Our modern day sedentary lifestyle and unhealthy dietary habits are an open invitation for diseases among which Hypertension and Diabetes are most common and life threatening in long term. Therefore, it is essential that we are aware of so-called Heart friendly food items so that we can inculcate them in our eating habits. Before going further we have to know what normal blood pressure is and what is hypertension [1].

Certain dietary facts which one has to be aware of for good cardiac health are:- 1) Increase sodium content in diet can lead to early development of hypertension and can further aggravate it. The recommendation for daily sodium intake is 1,500 to 2,300 mg a day [3]. 2) Increase potassium content will keep a check on high blood pressure [4]. Potassium rich foods should be encouraged instead of supplementation. 3) Low Calcium content in the diet is again a risk factor for the development of heart diseases. Recommended dietary intake of calcium is 1000-1200 mg daily [5]. 4) Increase fatty food in the diet will lead to weight gain which is again directly proportional to the blood pressure [6]. 5) LDL Cholesterol is bad for the heart

whereas HDL Cholesterol is Heart Friendly. Therefore, food items should be demarcated on basis of presence of type of Cholesterol before consumption [7].

Table 1: Classification of Hypertension [2]

Blood Pressure Classification	Systolic Blood Pressure(in mm Hg)	Diastolic Blood Pressure(in mm Hg)
Normal	120	80
Pre hypertensive	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥160	≥100

Table 2: The DASH Diet (Dietary Approaches to Stop Hypertension)[8]

Food Group Daily Servings Significance to the DASH Diet

<ul style="list-style-type: none"> Grains and grain products ,7 – 8 in no.'s , Carbohydrates and fiber
<ul style="list-style-type: none"> Vegetables ,4 – 5 in no.'s, rich in Potassium, magnesium and fiber
<ul style="list-style-type: none"> Fruits ,4 – 5 in no.'s , rich in Potassium, magnesium and fiber
<ul style="list-style-type: none"> Low-fat milk products or fat free milk ,2 – 3 in no.'s , rich in Calcium, protein, potassium and magnesium .
<ul style="list-style-type: none"> Meats, poultry and fish 2 or less in no.'s, rich in Protein and magnesium
<ul style="list-style-type: none"> Nuts, seeds and beans 4 –5 in no.'s a week, rich in Magnesium, potassium, protein and fiber

Angiotensin converting enzyme inhibition is one of the important mechanism in Renin angiotensin aldosterone system which inturns plays a crucial role in regulating the blood pressure[9].Over-activation of the renin-angiotensin system is a risk factor for the development of hypertension. Compounds, such as anthocyanins and quercetin, which are found in apple peel have antihypertensive effects and is beneficial for decreasing of blood pressure level [10].When ACE is inhibited, it relaxes the blood vessels leading to decrease in blood pressure. It is believed that an Apple peel /skin extract is rich in flavonoids which exhibits ACE inhibitory properties [11].Apples also reduces the risk of cancers, cardiovascular disease, asthma, Hypercholesterolemia, and diabetes. Phytochemicals such as quercetin, catechin, phloridzin and chlorogenic acid, all

component of an apple are strong antioxidants[12].A Finnish study established that the Apple flavonoid content is inversely proportional to the coronary mortality. As per his study there was 43% cardiac risk reduction in women and 19%reduction in male coronary mortality[13].An Apple review was conducted which revealed that Apple consumption in a normal person improves his endothelium function[14].This is due to the flavonoids, such as quercetin and (-)-epicatechin, present in an apple which can increase nitric oxide and reduce endothelin-1 concentrations thus improving endothelial function and a better cardiac health[15].A study by a French Scientist also demonstrated reduction in atherosclerotic lesions in rats by 38% when put on a diet rich in apple extracts[16].To understand the benefits of a raw apple with skin, it is essential that we must first know the composition on an apple.

Table 3 : Apple Dietary value, per 100-gram edible portion[17]:% Of US RDA*

Vitamin A -1.8	Niacin-0.6	Phosphorus-1.2
Thiamine,B1-2.1	Vitamin C -16.0	Iron-3.0
Riboflavin,B2 -1.2	Calcium -0.9	Potassium-2.3
Water(%) - 85	Carbohydrate(%) -14	Calories - 56
Fat(%) - 0.6	Protein (%) -0.2	Crude fibre (%) -1

*Percent of recommended daily allowance set by FDA, assuming a 154 lb male adult, 2700 calories per day.

Apples are one of the main dietary source of antioxidants, phenolic compounds such as flavinoids [18].Flavonoids reduces the risk of cardiovascular disease by increasing the release of endothelial nitric oxide (NO) and inducing vasodilatation [19]. Anthocyanidins also protects the LDL cholesterol oxidation through their high antioxidant action [20]. Flavonoids are group of polyphenols which are mainly found in higher plants. Some of the other sources of flavonoids are apples, tea, wine, onion, oranges, and grapes. Till date more than 4000 flavonoids have been identified in plants [21].Biosynthesis of flavonoids occur by Shikimic acid pathway and Malonic acid pathway[22].Based on structural differences , flavonoids are classified in 6 subtypes which are –Flavanones, Flavones, Flavonols, Flavan-3-ols, Isoflavones and Anthocyanins [23]. Flavonoids as vasodilators are an area of great interest as far as cardiac health is concerned . There are studies indicating

that biflavones and isoflavones can enhance blood circulation in brain. A study illustrates that polyphenols from dietary sources bind to the red blood cells and prevent them from oxidative stress [24]. Flavanoids also possibly acts as antioxidant, antithrombotic, ant ischemic, antiarrhythmic, and most importantly antihypertensive agents [25]. Cytotoxicity and capacity to interact with enzymes through protein complex formation determines the biological function of the flavonoids. Some flavonoids acts as scavengers of free radicals such as reactive oxygen species (ROS), as well as chelating metals that generate ROS via the Fenton reaction[26]. Dietary polyphenols undergoes extensive modification during first-pass metabolism so that the forms reaching the blood and tissues are not the same as the dietary source[27]. There are certain evidence that consumption of apples and its juice can alter some blood biomarkers [28], which may produce various health benefits. Moreover, there are data suggesting that rather than antioxidant capacity, some concentrations of metabolites of dietary phenolic compounds may effect the cells through intracellular signalling which is important for cellular functions such as growth& proliferation[29]. It was determined that flavan-3-ols and procyanidins inhibit the angiotensin I converting enzyme (ACE) activity[30]. Hence it can be concluded that flavonoids rich diet along with DASH meal plan is more useful in mild form or early stages of hypertension than the conventional drugs[31]. Flavonoids reduces the risk of cardiovascular disease by lowering LDL cholesterol level and by preventing clumping of blood platelets which reduces the clotting of blood keep a check on formation of atherosclerotic plaques on arterial walls [32]

A study was conducted to demonstrate vasorelaxant property of flavonoids extract from a plant source and it showed flavonoids caused smooth muscle relaxation as well as inhibition of calcium influx in rats[34]. Flavan-3-ols exhibits several health benefits due to its cardioprotective action and also acts as antioxidant, anticarcinogen, antimicrobial, anti-viral, and neuro-protective agents[35]. Several Research suggest that apple peel or skin has more antioxidant content or property than the pulp or the whole fruit[36]. This antioxidant property comes from components such as Quercetin, , rutin, epicatechin, and catechin [37]. Most abundant polyphenols are incompletely absorbed in humans and their circulating levels may be low. Antioxidant capacity of apples is mostly present in the peel[38]. A study also showed that theunripe apples along with its seeds and peel are a great source of polyphenols. Also it established that antioxidant action of an apple was

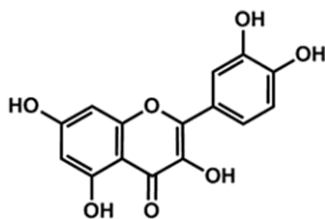
indirectly proportional to its maturity and ripening[39]. Apple peel is found to have more antioxidant activity than Vitamin C mainly due to the presence of quercetin-3-O-beta-D-glucopyranoside, most predominant form of Quercetin found in an apple peel[40]. As per a study Quercetin can inhibit LDL oxidation more effectively than even Vitamin C and alpha-tocopherol[41]. The other forms of quercetin in apple peel include quercetin O-arabinoside, 3-O-galactoside, 3-O-glucoside, and 3-O-rhamnoside[42].

Table 4: Subclasses of flavonoids and selected compounds [33]

1) Flavanols	Isorhamnetin, Kaempferol, Myricetin, Quercetin
2) Flavones	Apigenin, Luteolin
3) Flavanones	Eriodictyol, Hesperetin, Naringenin
4) Flavanonol	Taxifolin
5) Flavan-3-ols/Proanthocyanidins	Catechins, Gallocatechin, Epicatechins, Theaflavins
6) Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin

QUERCETIN

Quercetin is a flavanol belonging to flavonoids group, found in variety of plant derived foods items such as apples, onions, red wine, black and green tea etc. In 1990, studies were conducted claiming that quercetin intake in diet was indirectly proportional to occurrence of cardiovascular diseases[43]. Quercetin is a type of flavonoid found in an apple peel and it is said to lower blood pressure by its antioxidant effects, angiotensin-converting enzyme inhibition and improved endothelium function[43,44]. In a study, hypertensive people taking Quercetin supplements (730 mg/day) noticed reduction in their systolic blood pressure by approximately 7 units (mmHg) and diastolic pressure by 5 units (mmHg) in prehypertensive and stage 1 hypertensive subjects. This study established that Quercetin intake reduces the coronary mortality[45]. There was a study conducted in 2010 in which Quercetin and one of its metabolite were used to demonstrate that the third phase of flavonoid metabolism is mediated by platelets and that the flavonoid metabolites can inhibit the function of platelets.[46]



Molecular Formula for Quercetin is $C_{15}H_{10}O_7$

Figure 1 : Quercetin Chemical Structure[47]

A double blinded, placebo-controlled, crossover study where they have demonstrated that Quercetin has important vasorelaxant properties on isolated arteries and lowers blood pressure in the spontaneously hypertensive rat[48]. There are clinical studies claiming that flavonoid-rich foods can improve endothelial function in hypertensive patients[49]. Quercetin is also believed to be particularly helpful in reducing systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight patients with a high-cardiovascular disease risk[50]. Now that we know that Quercetin has a crucial role as an antihypertensive agent, it would be interesting to understand its metabolism and the mechanism behind its antihypertensive property.

Quercetin glycosides are rapidly hydrolyzed to generate quercetin aglycone during passage across the small intestine. It further undergoes phase II reactions into the glucuronidated and/or sulphated derivatives. Studies using rodents have depicted that oral quercetin is metabolised before accumulating in plasma[51,52]. Q3GA, an active metabolite of Quercetin helps in prevention of arteriosclerosis thus preventing cardiovascular disease including hypertension[53]. It is also believed that Antihypertensive effect and improved endothelial function by Quercetin is due to increased NOS activity and decreased superoxide anion (O_2^-) generation along with inhibition of p47 expression[54]. A recent study in 2012 also suggested that Quercetin released from its glucuronidated metabolites may be responsible for its hypotensive action by causing vasorelaxation [55]. There are various studies claiming that dietary supplementation of Quercetin which is present in high concentration in an apple peel along with certain lifestyle modifications is beneficial for Stage 1 Hypertensive patients. Another component of an apple peel which is being researched upon for its Antihypertensive effects is Proanthocyanidins.

Proanthocyanidins: Proanthocyanidins (PAs) are metabolites of the flavonoid pathway where flavan-3-ols,

catechin, and epicatechin initiates its synthesis. Anthocyanins and flavonols are also generated by the same pathway. The flavonoid biosynthetic pathway is found to be most predominant in an apple peel/skin [56]. Proanthocyanidin are secondary plant metabolites having antioxidant activity and they consist of PCOs (proanthocyanidin oligomers) or OPCs (oligomeric proanthocyanidins), which were discovered by Prof. Jacques Masquelier in 1947. Other than apples they are also found in berries, wines, chocolates, onions, tea, cinnamon and Ginkgo biloba[57]. Apples contain about eight times the amount of proanthocyanidin found in wine[58]. The possible mechanism by which Proanthocyanidin helps in lowering the blood pressure is that it suppresses production of a protein endothelin-1 that constricts blood vessels[59]. It is also believed to induce vasodilation as a result of increased NO production, reduced platelet aggregation and LDL oxidation[60]. Antioxidant property of proanthocyanidins can be understood by the fact that it interacts with the phospholipids, which restricts the access of oxidants on the membrane surface and movements of oxidants within the membrane[61]. Proanthocyanidins are very strong antioxidants and thus act as anti-cancer and anti-allergic agents, and also improve the heart health. Many studies have shown that proanthocyanidins help to prevent the oxidation of LDL cholesterol, reduce blood pressure and improve fat metabolism. They also prevent cardiovascular disease by reducing the risk associated with high blood cholesterol[62]. A study was conducted using rat aortic endothelial cells which concluded that procyanidin C1 promotes Ca^{2+} -mediated signals like hyperpolarization via activation of multiple K^+ channels and by releasing Nitric Oxide therefore suggesting that procyanidin C1 is efficacious in treating cardiovascular diseases [63].

Resveratrol which is a natural phenol, is said to prevent endothelial cell damage of human coronary artery and protect heart against oxidative stress[64].

Pectin is a soluble fiber which is found in apples and other citrus fruits. Also it is found in the cell walls of many plants. Apple pectin may help lower blood pressure, in addition to other health benefits. Apple pectin is said to have better cholesterol lowering effect than other pectins including orange pectin[65]. A study showed that Apple pectin helps in improving the cholesterol profile by inhibition of the plasma cholesteryl ester transport protein (CETP)[66]. Pectin has two forms, insoluble and water soluble[67]. The insoluble part of Pectin improves bowel health by increasing the bulk and water content of the

bowel. The water soluble fiber in apple pectin is converted into gel form in the gut. The gel fibres then normalizes the blood sugar, blood pressure and also reduces cholesterol absorption. Degree of methoxylation contributes to the Gel forming properties in apple pectin[68]. Also it is proved that the high methoxyl pectins inhibit more glucose uptake than the less methoxylated ones[69,70]. Dietary fiber is beneficial for the majority of heart related conditions and obesity in general. The same has been supported by the various studies demonstrating the effects of dietary fibres on body weight management[71], plasma cholesterol and lipoprotein levels[72,73] and lowering of blood sugars levels. Studies claim that fiber consumption is inversely proportional to body weight[74]. In an experiment conducted on rats, it was observed that the intake of a HMAP-enriched diet led to a decrease in body weight, stabilization of blood sugar levels, cholesterol reduction mainly triglycerides and a better lipid profile[75]. Though direct effect on blood pressure could not be demonstrated but all the above mentioned effects specially weight loss and reduction of cholesterol eventually effects the blood flow of a person and his cardiac status. So one can indirectly conclude that high methoxylated Apple pectin exhibits antihypertensive properties as well.

Anthocyanins another content of an apple peel, are a group of flavonoids found in the plant based foods, and is responsible for the colour of many fruits and vegetables like cherries, red grape and red cabbage etc[76]. The possible mechanisms for its cardiac friendly actions are they reduced platelet coagulability. Also they inhibit lipoprotein oxidation, reduces risk factors for atherosclerosis and are good antioxidants [77].

Other ACE Inhibitors derived from natural sources : They can be divided into three categories as animal-derived, plant-derived and microorganism-derived peptides[78,79]. **Animal-derived** category includes peptides from milk, meat, fish and eggs. Fishes like bonito, sardine, salmon, tuna etc. are used for derived ACE inhibitory peptides.

Plant-derived peptides-Sources including soybean, flaxseed, sunflower, rice and corn. Some of the herbs which acts as antihypertensive agent are lime blossom, Kudzu, Garlic, Hibiscus tea, Saffron, Lajju extract, Stevioside, Green coffee bean extract, Cocoa powder etc[80]. A study indicates that the increased intake of flavonoids in form of apples can cause a decrease in mortality from cardiac causes specially in

postmenopausal women[81]. Another French study indicated that diets rich in total dietary fiber and nonsoluble dietary fiber like apples, lowered the risk factors of several heart disease like blood pressure and cholesterol levels[82]. Researchers at the University of California-Davis report suggested that daily consumption of apples and apple juice may help reduce the damage caused by LDL cholesterol and protect against heart disease[83].

CONCLUSION

It can be concluded that an apple peel is a rich source of flavonoids. These flavonoids such as Quercetin, proanthocyanidins, anthocyanins and pectin content of an apple directly or indirectly benefits the cardiovascular system and helps in lowering of blood pressure. Most of these flavonoids exhibits their action by inhibition of angiotensin converting enzyme, improving endothelial function of blood vessels, preventing oxidation of low density lipoprotein and improving high density lipoprotein in circulation, prevent atherosclerosis and are strong antioxidants.

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