TOMATO EXTRACT AS AN ANTI-HYPERTENSIVE AGENT TO MODULATE BLOOD PRESSURE

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ABSTRACT
Hypertension is the leading cause of cardiovascular disease. Tomatoes can make people healthier and decrease the risk of conditions such as cancer, osteoporosis and cardiovascular disease. Taking tomatoes and tomato products could reduce the risk of cardiovascular diseases because of lycopene in it. Red ripened tomato is a powerful antioxidant, Vitamin E and lycopene in tomato prevents LDL oxidation effectively. Tomatoes contain a great deal of Vitamin A and Vitamin C. Tomatoes are rich in potassium, which is known to reduce blood pressure. Lycopene extract from tomatoes is obtained by ethyl acetate extraction of the pulp of ripe red tomatoes. Provided herein is technology related to compositions and uses related to anti-hypertensive agents in tomatoes. Essential hypertension can be treated with one of several types of medications, including diuretics, β-adrenoreceptor blockers, inhibitors of angiotensin converting enzyme, calcium channel blockers, vasodilators and centrally acting agents. Vitamin C has effectively resulted in proper dilation of blood vessels in the cases of congestive heart failure, high cholesterol, angina pectoris and high blood pressure. It was discovered that sugar free tomato extracts exhibits an ability to reduce ACE activity.

KEYWORDS: Hypertension, Tomato, Lycopene, Antioxidant.

INTRODUCTION
Essential hypertension (EHT), one of the most prevalent chronic diseases, affects nearly a billion People all over the world. It is also a risk factor of cardiovascular morbidity and mortality.⁷
Experimental studies have provided strong evidence that oxidative stress, inflammatory processes, endothelial dysfunction and subsequent vascular remodeling have a tight relationship with the pathogenesis of hypertension, especially the role of oxidative stress has been testified by both animal models and human-based studies\cite{1,2}. Oxidative stress could inactivate nitric oxide, impairing endothelium-dependent vasodilatation\cite{3}, which suggested that inhibition of oxidative stress might be one effective method controlling blood pressure (BP).

Essential hypertension is not caused by a single identifiable cause but by a cluster of factors, including heredity, age, body weight, environment and diet. Treatment of moderate to severe hypertension is a life-long commitment and requires drug therapy in combination with changes in lifestyle, including weight reduction if overweight, limitation of alcohol and reducing salt and fat intake. Essential hypertension can be treated with one of several types of medications, including diuretics, β-adrenoreceptor blockers, inhibitors of angiotensin converting enzyme (ACE), calcium channel blockers, α-adrenoreceptor blockers, vasodilators, and centrally acting agents.

The renin-angiotensin system is a powerful mechanism for controlling blood pressure. When blood pressure falls, the kidneys undergo several intrinsic reactions converting pro-renin to renin. When renin enters the bloodstream, it hydrolyzes plasma angiotensinogen to release a peptide called angiotensin I. When angiotensin I circulates to the small vessels of the lungs, it is immediately hydrolyzed to release an 8-amino acid peptide, angiotensin II, by ACE. Angiotensin II circulates in the blood before it is inactivated by angiotensinase. Angiotensin II is a very potent vasoconstrictor and raises blood pressure by severely constricting the arteries, causing an increase in peripheral resistance. It is also able to act on the kidneys to retain both salts and water, leading to an increase in the extracellular fluid volume and thus produces an increase in blood pressure. Finally, angiotensin II causes the adrenal glands to release aldosterone, which in turns increases reabsorption of water and salt in the kidneys\cite{4}.

Thus, one approach to control blood pressure is by treatment with ACE inhibitors. ACE inhibitors block the formation of angiotensin II, which normally causes blood vessels to narrow and blood pressure to increase. ACE is not specific for converting angiotensin I to angiotensin II. In addition to its actions on angiotensin, ACE also cleaves a number of other peptides including bradykinin, a non peptide. Bradykinin is a potent endothelium-dependent vasodilator, which causes natriuresis and a consequent drop in blood pressure. ACE inhibitors
not only decrease the formation of angiotensin II, but also increase the amount of bradykinin, thus further lowering blood pressure.[4]

Tomatoes are a member of the deadly nightshade family, the red pigment contained in tomatoes is called lycopene. This compound appears to act as an antioxidant, neutralizing free radicals that can damage cells in the body. Only recently, studies have revealed that lycopene may have twice the punch of another well-known antioxidant beta-carotene. Lycopene is located in the cell wall of the tomato, so by cooking in a bit of oil, this healing compound is more fully released. In addition cooking the tomato in olive oil allows your body to absorb the lycopene better.[5]

Lycopene, one of the most powerful antioxidants and free radical quenchers, has received attention for its pivotal role in inhibiting oxidative stress, improving vascular function and preventing cardiovascular disease in humans.[6] However, intervention trials investigating the role of lycopene supplementation or lycopene-containing foods in regulating BP had deduced conflicting results. Several studies demonstrated that at least four weeks of daily oral supplementation with tomato extract or tomato juice significantly decreased BP.[6,7] Lycopene (4.5 mg/day, 4 weeks) could elevate BP.[8] One meta-analysis investigating the effect of lycopene on BP had concluded that lycopene treatment could effectively decrease SBP, but had no statistical effect on DBP. As the half life of serum lycopene is about 14 days, the active metabolites and their varying tissue levels may be of importance[9] and the wash-out period may alleviate the effect of lycopene during the treatment of placebo.

Provided herein is technology related to compositions and uses related to anti-hypertensive agents in tomatoes. It was discovered that sugar free tomato extracts exhibits an ability to reduce ACE activity.

Treatment” refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. As used herein, "therapeutically effective dose" refers to an amount of a therapeutic agent sufficient to bring about a beneficial or desired clinical effect. Said dose can be administered in one or more administrations. However, the precise determination of what would be considered an effective dose may be based on factors individual to each patient, including, but not limited
to, the patient’s age, size, type or extent of disease, stage of the disease, route of administration, the type or extent of supplemental therapy used, ongoing disease process and type of treatment desired (e.g., aggressive versus conventional treatment).[4]

**TOMATO EXTRACTS**

Tomato extracts having activities that are beneficial for cardiovascular health. For example, the tomato extract decreases ACE activity in normal serum in a dose dependent manner. In addition, the active compounds in the tomato extract are water-soluble and have a very different structure that the lipid-soluble compounds. The extract can be fractionated to isolate one or more active fractions therein by, for example, molecular weight filtration or chromatography on a suitable support. The fractionation, e.g., using a Lipidex-1000 column, results in the removal of lipids. The extract was also fractionated by solid phase extraction. During the development of the technology provided, experiments carried out on tomato extract revealed that the active components of the extract pass through an ultra filtration membrane having molecular weight cut-off 1000 Da. In addition, the active extract is colourless, water soluble and does not lose activity when boiled.[4]

**Chemical Composition of* Solanum lycopersicum***

There are known different varieties of tomato, round, oval, "cherry", but all have the same nutritional characteristics, being an important source of: - potassium, phosphorus, magnesium, iron, so necessary to the normal activity of nerves and muscles.

- Vitamins as A, B and C - tomatoes is the third source of vitamin C in our diet and the fourth for vitamin A through its content in beta-carotene or pro vitamin A.
- Phytosterols, compounds that help to keep cholesterol under control.
- Folic acid, which helps eliminate homocysteine, an amino acid whose metabolism is dependent on the metabolism of vitamins from B complex, especially that of folic acid.[5]

Despite the clear-cut effects of the tomato extract, it remains mysterious why it lowers blood pressure so profoundly. Direct effects on blood pressure of lycopene, beta-carotene, folate, vitamin C and vitamin E have not been described. However, tomatoes are rich in potassium, which is known to reduce blood pressure. Tomatoes also contain polyphenolic compounds, the flavonoids. Recently, we found that tomato paste lowers blood pressure in spontaneously hypertensive rats. This effect was greater when we administered tomato paste obtained from transgenic tomatoes which had a higher concentration of the flavonoids quercetin-glycoside,
rutin. Several mechanisms have been suggested that could explain this effect of flavonoids. Flavonoids can protect the vasorelaxant NO radical from reaction with the superoxide anion radical (O$_2$ •$-$) because these polyphenols are scavenger of (O$_2$ •$-$). In this way not only the NO effect is preserved but also the formation of the very reactive damaging peroxynitrite molecule is prevented. Flavonoids can efficiently scavenge the damaging peroxynitrite.$^{[11]}$ They are also known to inhibit the (O$_2$ •$-$) producing enzyme xanthine oxidase.$^{[12]}$ Finally, polyphenols may increase the availability of l-arginine, which can be a rate-limiting factor for the production of NO, by inhibiting arginase activity.$^{[13]}$ Antioxidants act synergistically, i.e. their combined effect is larger than the sum of the individual components. It will be interesting to see whether the tomato contains such a synergistic combination of compounds.$^{[10]}$

Lycopene extract from tomatoes is obtained by ethyl acetate extraction of the pulp of ripe red tomatoes with subsequent removal of the solvent. The major colouring principle in tomato extract is lycopene; however, minor amounts of other carotenoid pigments may also be present. The product also contains oils, fats, waxes and flavour components naturally occurring in tomatoes.$^{[14]}$

**Chemical formula:** C$_{40}$H$_{56}$ (lycopene).

**Formula weight:** 536.85 (lycopene).

**Structural formula$^{[14]}$**

![Chemical structure of lycopene](image)

All-trans-lycopene, the major colouring principle, Dark-red viscous liquid.

**Solubility$^{[14]}$**

Freely soluble in ethyl acetate and n-hexane; partially soluble in ethanol and acetone; and insoluble in water.
Assay
Not less than 5% and not more than 15% total lycopene. Not less than 6.5% and not more than 16.5% total carotenoids. (Calculated as lycopene).

Tomatoes provide essential antioxidants\textsuperscript{[5]}
Tomatoes contain a great deal of Vitamin A and Vitamin C. This is primarily because these vitamins and beta-carotene work as antioxidants to neutralize harmful free radicals in the blood. Free radicals in the blood stream are dangerous because it may lead to cell damage. Remember, the redder the tomato you eat is, the more beta-carotene it contains. In addition, you also want to keep in mind that cooking destroys the Vitamin C, so for these benefits, the tomatoes need to be eaten raw.

Antioxidants are substances (vitamins, minerals, natural coloring) that protect body cells from the harmful effects of free radicals, molecules that form in the body through contact with oxygen. Free radicals are partly responsible for the processes of aging, cardiovascular diseases and cancer and act by attacking the cell membranes and the cellular DNA. Cellular oxidation is a normal process that affects all tissues, is inevitable, but some factors such as environmental contamination, smoking, diets high in saturated fats, excessive sun exposure and excess physical activity contribute to increased production of free radicals. Most antioxidants are found in plants, which is why it is so necessary to eat more fruits and vegetables as they protect us from free radicals naturally. It is recommended a weekly consumption of 7 servings of tomato derivatives, (one serving = one glass of tomato juice of 250 ml or 125 ml of tomato sauce for other dishes).

Benefits of Tomato\textsuperscript{[5]}
Tomatoes are good for your heart
Because of the Vitamin B and potassium in tomatoes, they are effective in reducing cholesterol levels and lowering blood pressure. Therefore, by including tomatoes in your regular balanced diet you can effectively prevent heart attacks, strokes as well as many other heart related problems that may threaten your life.

Lower Cholesterol
A Tomato- cholesterol free and a good source for diet; it won’t add cholesterol to the diet. A cup of tomato provides 9% of fiber that helps you to lower the high cholesterol levels.
Tomatoes also contains niacin (vitamin B$_3$), which has been used as a safe way to lower cholesterol levels.

**Treatment of Vasodilation**
Vitamin C has effectively resulted in proper dilation of blood vessels in the cases of atherosclerosis, congestive heart failure, high cholesterol, angina pectoris and high blood pressure. It has been found that supplements of vitamin C improve blood vessel dilation.

**Lower Blood Pressure**
The tomatoes provide significant drop in blood pressure. After 8 weeks, ongoing tracking of daily tomato ingestion (in the form of lycopene complex – a tomato extract) showed a drop in both the blood pressure top number (systolic) by 10 points and the bottom number (diastolic) by 4 points.

**Reduce Heart Disease**
Tomatoes are good source of potassium that have been shown to lower high blood pressure and reduce risk of heart disease. Vitamin B$_6$ and folate, present in tomatoes, are needed to the body to convert a dangerous chemical called homocysteine into other, benign molecules. High levels of homocysteine can directly damage blood vessel walls and are associated with an increased risk of heart attack and stroke.

**CONCLUSION**
Tomato lowers the blood pressure and risk of heart disease. Effectiveness of tomatoes in lowering blood pressure is attributed to lycopene, a chemical present in tomato. Tomato extract contains carotenoids such as lycopene, beta carotene and vitamin E, (known as effective antioxidants) to inactivate free radicals and to slow the progression of atherosclerosis.

**REFERENCES**


