Taking tomatoes to heart

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Abstract

There is compelling evidence for tomatoes to be considered as a cardiovascular protective food, due to the presence of many nutrients which have been associated with its perceived and/or proven effects on the cardiovascular system. However, despite an inverse association found for high intake of tomato-based products, dietary lycopene has not been strongly associated with reduced risk of cardiovascular disease (CVD). This indicates that other unidentified compounds in tomatoes may have...
cardioprotective effects. We identified potent anti-platelet factors in tomato extracts, which inhibited platelet aggregation. Platelets play a critical role not only in haemostasis but also in the pathological development of cardiovascular diseases. There is increasing evidence that acute clinical manifestations of coronary atherosclerotic disease are caused by plaque disruption and subsequent platelet-thrombus formation. Platelet activity can influence the progression of disease as well as the stability of atherosclerotic plaques. We hypothesise that observed cardiovascular benefits attributed to the tomato could be linked to antiplatelet activity and thus suppression of platelet function in vivo. This type of natural anti-thrombotic agent could have an application in primary prevention of CVD.

Introduction

During the last half-century, the fruit of the cultivated tomato (Lycopersicon esculentum) has become a popular and highly consumed food (Canene-Adams et al. 2005). Tomato is a rich source of folate, vitamin C, and potassium (Blum et al. 2005; Mancini et al. 1995). Tomato also contains several other components that are beneficial to health, including vitamin E, trace elements, flavonoids, phytosterols, and several water-soluble vitamins (Agarwal and Rao 2000; Mancini et al. 1995; Verhoeyen et al. 2002). Moreover, the antioxidant activity of lycopene as well as several other carotenoids and their abundance in tomato, makes it a rich source of antioxidants (Agarwal and Rao 2000; Mancini et al. 1995; Verhoeyen et al. 2002). In addition, consumption of vitamin A precursors such as beta- and gamma-carotene present in modest levels within tomato or tomato-based foods make this fruit rich in supply of vitamin A activity.

Individuals in the Mediterranean area have a lower risk of several important chronic diseases, including cardiovascular disease (CVD) and a number of types of cancer (breast, colon, and prostate cancer) when compared with their North American and other European counterparts (Agarwal and Rao 2000; Rissanen et al. 2002). These differences may be associated with nutritional traditions. Consumption of tomatoes appears to be one such tradition that may account for the lower risk associated with diseases in people from this geographical area. In addition to vitamins and antioxidants, tomatoes also have water soluble anti-platelet compounds, capable of inhibiting platelet aggregation both in vitro and in vivo (Duttaroy et al. 2001). Therefore, presence of both antioxidants and anti-platelet factors makes tomato a beneficial fruit in preventing CVD. There are several excellent reviews available on the overall health benefits of tomatoes (Agarwal and Rao 2000; Canene-Adams et al. 2005; Giovannucci 1999; Sesso et al. 2005; Weisburger 2002; Wilcoxon et al. 2003); however, this review will focus mainly on the beneficial effects of tomatoes on cardiovascular health.

Epidemiology and intervention studies

There is epidemiological evidence that consumers of tomatoes have a lower risk of many types of chronic diseases, including CVD and different forms of cancer (Agarwal and Rao 2000; Cockey 2002; La 1998; Zackheim 1999). Evidence in support of the role of lycopene in the prevention of CVD stems primarily from epidemiological observations on normal and at-risk populations (Giugliano 2000; Maruyama et al. 2001; Olfer’ev et al. 2004; Rao 2002; Rissanen et al. 2003). Geographic pathology has
produced important data which shows that populations with a regular intake of tomato products, such as those found in the Mediterranean region, have a lower incidence of chronic diseases in particular, CVD (Weisburger 2002). In recent epidemiological studies, tissue and serum levels of lycopene, a carotenoid available from tomatoes, were inversely related to the risk of CVD. Antioxidant properties of lycopene have been suggested as being responsible for the beneficial effects of tomatoes and tomato-based products (Agarwal and Rao 2000). Lycopene has been suggested to have several mechanisms of action including inhibition of LDL oxidation (Heber and Lu 2002). Lycopene is an open-chain hydrocarbon containing 11 conjugated and two non-conjugated double bonds arranged in a linear array. Lycopene, because of its high number of conjugated dienes, is the most potent singlet oxygen quencher among the natural carotenoids (Arab and Steck 2000). Although evidence for a relationship between in vitro LDL oxidation and risk of CVD is not fully established, LDL oxidation is now recognized as representing an important early event in the development of atherosclerosis.

The strongest population-based evidence for the beneficial effects of lycopene comes from a recently reported multi-centre case-control study (EURAMIC) that evaluated the relationship between adipose tissue antioxidant status and acute myocardial infarction. Subjects (662 cases and 717 controls) from 10 European countries were recruited to maximize variability in exposure within the study. After adjusting for age, body mass index, socioeconomic status, smoking, hypertension, and maternal and paternal history of the disease, only lycopene, and not ß-carotene levels was found to be protective against CVD (Kardinaal et al. 1993; Kardinaal et al. 1995; Kohlmeier et al. 1997). The protective potential of lycopene was maximal among individuals with the highest polyunsaturated fat stores (Kardinaal et al. 1995). In a cross-sectional study comparing Lithuanian and Swedish populations showing diverging mortality rates for CVD, lower blood lycopene levels were found to be associated with increased risk and mortality from CVD (Kristenson et al. 1997). In an Austrian stroke prevention study, lower levels of serum lycopene and α-tocopherol were reported in individuals from an elderly population at high risk for microangiopathy-related cerebral damage (Schmidt et al. 1997). Although the epidemiological studies conducted so far provide convincing evidence for the role of lycopene in CVD prevention, it is at best only suggestive and not proof of a causal relationship between lycopene intake and risk of CVD. Such proof can be obtained only by performing controlled clinical dietary intervention studies where both the biomarkers of the status of oxidative stress and the disease are measured. To date, very few such intervention studies have been reported in the literature. In one study, where healthy human subjects consumed a lycopene-free diet for a period of 2 weeks, their serum lycopene levels decreased by 50% by the end of week 2 and, at the same time, an increase of 25% in in vivo lipid oxidation was observed (Allen et al. 2003). In a small dietary supplementation study, six healthy male subjects consumed 60 mg/day lycopene for 3 months (Fuhrman et al. 1997). At the end of the treatment period, a significant 14% reduction in their plasma LDL cholesterol levels was observed (Fuhrman et al. 1997). In a randomized, crossover dietary intervention study, 19 healthy human subjects (10 male and 9 female), non-smokers, not on any medication and vitamin supplements, consumed lycopene from traditional tomato products and nutritional supplements for 1 week. Although there were no changes in serum total
cholesterol and LDL and HDL cholesterols, serum lipid peroxidation and LDL cholesterol oxidation were significantly decreased as the serum lycopene levels increased (Agarwal and Rao 1998). However, despite an inverse association found for high intake of tomato-based products, dietary lycopene was not strongly associated with the risk of CVD. This indicates that other unidentified compounds in tomatoes may have cardio-protective effects.

**Beneficial effects of tomatoes on the cardiovascular system**

**a. Atherosclerosis**

Although genetic factors and age are important in determining risk, several other factors, including hypertension, hypercholesterolemia, insulin resistance, smoking and diet are also major risk factors associated with CVD (King 2005; Pearson *et al.* 2000; Roche *et al.* 2005; Tai and Tan 2005). Oxidative stress induced by reactive oxygen species (ROS) is also considered to play an important role in the aetiology of several chronic diseases, including CVD (Jialal and Fuller 1993; Molavi and Mehta 2004; Nuttall *et al.* 1999). Oxidation of circulating LDLs that carry cholesterol into the bloodstream to oxidized LDL is thought to play a key role in the pathogenesis of atherosclerosis, which is the underlying disorder leading to heart attack and ischaemic strokes (Jialal and Fuller 1993; Molavi and Mehta 2004; Nuttall *et al.* 1999). Antioxidant nutrients are believed to slow the progression of atherosclerosis because of their ability to inhibit damaging oxidative processes. Lycopene is one such dietary antioxidant that has received much attention recently. Other possible mechanisms include enhanced LDL degradation, LDL particle size and composition, plaque rupture, and altered endothelial functions. However, there is convincing evidence to indicate that ROS generated both endogenously and also in response to diet and lifestyle factors may play a significant role in the aetiology of atherosclerosis and CVD. Central to this oxidative hypothesis is oxidation of LDL as the primary initial step leading to its uptake by macrophages inside the arterial wall and, formation of foam cells and atherosclerotic plaque. LDL consists of a large molecular weight-protein, apolipoprotein B, neutral and polar lipids and, a mixture of lipophilic antioxidants including β-carotene and vitamin E. As a result of oxidative modifications of the native LDL molecule, several biologically active molecules can be formed, including protein adduct products with breakdown products of oxidized fatty acids that facilitate recognition of modified LDL by macrophage scavenger receptors. In addition to influencing the formation of foam cells and plaque in arterial walls, components of oxidized LDL (oxLDL) can also influence other events that are related to increased risk of CVD. These include their ability to: increase cholesterol accumulation by macrophages; produce proteins that are chemotactic to monocytes and cytotoxic to a variety of cells causing endothelial injury; alter gene expression in arterial cells leading to increased expression of colony-stimulating factors; increase expression of adhesion molecules at the endothelial cell surface; inhibit an endothelium-dependent relaxation factor and promote vasospasm; inhibit vasodilatation; increase binding to type I collagen and; enhance coagulation pathways and platelet aggregation. In addition, oxidised components of LDL can promote migration and proliferation of smooth muscle cells, formation of foam cells and fatty streaks in the arterial intima and, cause eventual rupture of arterial plaques. Therefore, inhibition of LDL oxidation may play an important in preventing CVD.
Some 725 middle-aged men, free of coronary heart disease and stroke, took part in a Kuopio Ischemic Heart Disease Risk Factor (KIHD) study. Men within the lowest quartile for serum levels of lycopene had a 3.3 fold increased risk of an acute coronary event or stroke as compared to other groups within the study (Rissanen et al. 2001). In a second study, association between plasma lycopene concentration and intima-media thickness of the common carotid artery wall (CCA-IMT) was examined (Rissanen et al. 2003). This research was part of an Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study, in which 520 asymptomatic men and women participated (Rissanen et al. 2000). It was found that low plasma levels of lycopene in men were associated with an 18% increase in IMT when compared with men whose plasma levels were higher than the median. In women, this difference was not significant (Rissanen et al. 2000; Rissanen et al. 2003).

A number of in vitro studies have shown that lycopene can protect native LDL from oxidation and can suppress cholesterol synthesis. In a J-774 A.1 macrophage-like cell line, lycopene treatment at a concentration of 10 µM, produced a 73% inhibition in cholesterol synthesis using [3H]acetate as a precursor (Fuhrman et al. 1997). A slightly lower inhibition of cholesterol synthesis was also observed with β-carotene. In this study, both of these carotenoids augmented the activity of the macrophage LDL receptor. However, in another study, dietary enrichment of endothelial cells with β-carotene but, not lycopene inhibited the oxidation of LDL (Dugas et al. 1999). Predictability of in vivo LDL oxidation as a marker of atherosclerosis or coronary heart disease has been questioned in recent years. In animal intervention studies where an increase in resistance of extracted LDL to in vitro oxidation was shown to occur, correlation to a reduced risk of atherosclerosis was not always observed. Use of well-defined subject populations, standardized outcome measures of oxidative stress and disease, and lycopene ingestion that is representative of a normal healthy dietary intake is essential for development of a meaningful interpretation of the results in terms of therapeutic applications. Some of the conflicting epidemiological observations being reported in the literature may be connected to issues related to lycopene absorption. In general, circulating and adipose tissue levels of lycopene seem to be better indicators of disease prevention than dietary intake data. Lycopene has been shown to be absorbed better from processed tomato products than from fresh tomatoes. Careful consideration must be given to all of these factors in designing future studies to evaluate the role of lycopene in the prevention of CVD.

b. Platelet function

Platelet aggregation is fundamental to a wide range of physiological and pathological processes, including the induction of thrombosis and arteriosclerosis (Duttaroy et al. 1989; Hamet et al. 1983; Kroll and Schafer 1989). Normal haemostasis is initiated when platelets are exposed to the sub-endothelial matrix, where they adhere to collagen via specific cell-surface receptors (Coller et al. 1995; Dutta-Roy et al. 1986; Kroll and Schafer 1989). This adhesion step is followed by platelet activation that is accompanied by synthesis and release of pro-aggregatory molecules such as thromboxane (Tx) A2 and ADP, which amplify platelet responses to collagen and recruit additional platelets to the site of injury (Coller et al. 1995; Duttaroy et al. 1986; Kroll and Schafer 1989). The concerted action of collagen, ADP, and TxA2 activates specific signalling pathways, generating a number of
second messengers and leads to functional expression of a GPIIb-GPIIIa complex of the fibrinogen receptor on the platelets (Coller et al. 1995; Duttaroy et al. 1986; Kroll and Schafer 1989). Pro-haemostatic mechanisms appear to be counterbalanced and regulated by a number of physiologic anti-haemostatic molecules that work in a concerted and redundant manner, resulting in the release of prostacyclin (PGI2), nitric oxide, and endothelium-dependent hyperpolarizing factor by the endothelium as well as ADP hydrolyzing activity associated with endothelial cell membrane apyrase (CD39) (Duttaroy et al. 1991; Duttaroy 1994; Duttaroy and Sinha 1987; Harker and Fuster 1986). Aggregation of platelets by agonists is mediated, in part, through the intracellular formation of prostaglandin (PG) G2, PGH2 and TxA2 from arachidonic acid, 20:4n-6 (AA) (Duttaroy et al. 1991; Duttaroy 1994). In contrast, PGI2, an arachidonic acid metabolite of endothelial cells, is the most potent natural inhibitor of platelet aggregation (Duttaroy et al. 1991; Duttaroy 1994). Prostaglandin-induced inhibition of platelet aggregation is mediated through an increase in cAMP synthesis due to activation of adenylate cyclase. Activation of adenylate cyclase is initiated by binding of PGI2 or PGE1 to specific platelet surface receptors. Alternatively, cAMP levels in platelets can also be increased by inhibiting cAMP phosphodiesterase activity (Duttaroy and Sinha 1987).

Hyperactivity of platelets and, their adhesion and aggregation at the site of injury in atherosclerotic vessel walls, is critically important to the pathogenesis of CVD (Duttaroy et al. 1986; Duttaroy 1994; Hamberg et al. 1974; Hamet et al. 1983). Furthermore, there is increasing evidence that acute clinical manifestations of coronary atherosclerotic disease are caused by plaque disruption and subsequent platelet-thrombus formation (Badimon et al. 1999; Falk et al. 1995). Coronary atherosclerotic lesions appear in early life and towards the end of the second decade of life; asymptomatic atherosclerosis lesions are present in most people living in industrialised societies. Platelet activity is thought to play a major role in the development as well as, in the stability of atherosclerotic plaques (Badimon et al. 1999; Falk et al. 1995). In support of the pathophysiological role of platelets, platelet inhibitory drugs such as aspirin have been observed to reduce the incidence of myocardial infarction, stroke and death from cardiovascular disease in secondary prevention trials (Schror 1997). However, the anti-platelet effects of aspirin are actually relatively weak and, the drug also has been shown to cause severe gastrointestinal disturbances and bleeding problems in some patients. Given the high incidence of cardiovascular disease in developed countries, there is great need for identification of effective anti-platelet compounds. These should inhibit platelet aggregation without increasing bleeding time (a problem associated with glycoprotein IIb/IIIa antagonists) in order to circumvent problems with ulcers in patients who are taking aspirin as a prophylaxis (Schror 1997). Recently, aspirin’s anti-platelet limitations have progressively underscored the critical need for improved platelet aggregation inhibitor therapy which is not only effective, but also safe and well tolerated. This concept has stimulated research into prevention of platelet hyperactivity by several means including dietary supplementation (Duttaroy et al. 1999; Duttaroy 2002; Pierre et al. 2005).

Effects of different fruit extracts on human platelet aggregation in vitro

We have demonstrated the presence of anti-platelet factors in tomatoes (Duttaroy et al. 2001; Duttaroy 2002). Table-1 shows the inhibitory effect of different fruit extracts
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Table 1. Effects of fruit extracts on inhibition of platelet aggregation in humans.

<table>
<thead>
<tr>
<th>Fruit</th>
<th>Scientific names</th>
<th>Family</th>
<th>% Fruit</th>
<th>% Inhibition of platelet aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomato</td>
<td><em>Lycopersicon esculentum</em></td>
<td>Solanaceae</td>
<td>100</td>
<td>70.0±12.0</td>
</tr>
<tr>
<td>Kiwi fruit</td>
<td><em>Actinidia delicosa</em></td>
<td>Actinidaeae</td>
<td>100</td>
<td>72.0±5.0</td>
</tr>
<tr>
<td>Grapefruit</td>
<td><em>Citrus paradisi</em></td>
<td>Rutaceae</td>
<td>100</td>
<td>44.2±8.1</td>
</tr>
<tr>
<td>Melon (Honeydew)</td>
<td><em>Cucumis melo</em></td>
<td>Cucurbitaceae</td>
<td>100</td>
<td>42.1±12.0</td>
</tr>
<tr>
<td>Strawberry</td>
<td><em>Fragaria virginiana</em></td>
<td>Rosaceae</td>
<td>100</td>
<td>33.1±7.0</td>
</tr>
<tr>
<td>Melon (Cantaloupe)</td>
<td><em>Cucumis melo cantaloupensis</em></td>
<td>Cucurbitaceae</td>
<td>100</td>
<td>27.5±11.0</td>
</tr>
<tr>
<td>Banana</td>
<td><em>Musa paradisiaca</em></td>
<td>Musaceae</td>
<td>50</td>
<td>22.4±4.5</td>
</tr>
<tr>
<td>Mango</td>
<td><em>Mangifera indica</em></td>
<td>Anacardiaceae</td>
<td>50</td>
<td>22.1±6.3</td>
</tr>
<tr>
<td>Pineapple</td>
<td><em>Ananas comosus</em></td>
<td>Bromeliaceae</td>
<td>100</td>
<td>19.8±9.4</td>
</tr>
<tr>
<td>Orange (Jaffa)</td>
<td><em>Citrus sinensis cv. Jaffa</em></td>
<td>Rutaceae</td>
<td>100</td>
<td>18.5±7.6</td>
</tr>
<tr>
<td>Grape (green)</td>
<td><em>Vitis vinifera</em></td>
<td>Vitaceae</td>
<td>100</td>
<td>16.4±8.9</td>
</tr>
<tr>
<td>Plum</td>
<td><em>Prunus domestica</em></td>
<td>Rosaceae</td>
<td>100</td>
<td>15.8±9.1</td>
</tr>
<tr>
<td>Grape (red)</td>
<td><em>Vitis vinifera</em></td>
<td>Vitaceae</td>
<td>100</td>
<td>13.8±7.8</td>
</tr>
<tr>
<td>Avocado</td>
<td><em>Persea americana</em></td>
<td>Lauraceae</td>
<td>20</td>
<td>12.1±4.5</td>
</tr>
<tr>
<td>Nectarine</td>
<td><em>Prunus persica nucipersica</em></td>
<td>Rosaceae</td>
<td>50</td>
<td>9.1±4.2</td>
</tr>
<tr>
<td>Apple</td>
<td><em>Malus domestica</em></td>
<td>Rosaceae</td>
<td>50</td>
<td>5.2±2.1</td>
</tr>
<tr>
<td>Pear</td>
<td><em>Pyrus malus</em></td>
<td>Rosaceae</td>
<td>100</td>
<td>2.0±2.0</td>
</tr>
</tbody>
</table>

on human platelet aggregation in vitro. The maximum inhibitory effect (70-75%) was found to be with tomato and kiwi fruit extracts whereas, apple and pear had very little activity (2-5%). Grapefruit, melon and strawberry had intermediate activities on platelet aggregation (33-44%). The pH of the different fruit extracts was acidic in nature; therefore the pH of our extracts was adjusted to pH 7.4 in order to avoid any effect of acidic pH on the platelet aggregation response. With the exception of avocado, apple, nectarine, banana and mango, a 100% juice (w/v) extract was used. A dose-dependent inhibition of platelet aggregation was observed for the tomato extract; maximum inhibition (72%) was obtained when 50 µl (100% juice) of tomato extract was added to 500 µl of prepared platelets. Most of the anti-platelet properties of tomatoes reside in the juicy part of the fruit. The anti-platelet potential of the fruits tested appeared to be opposite to that of their antioxidant activity which was reported earlier by Wang et al. (1996). According to the these authors, strawberry had the highest antioxidant capacity followed by plum, orange, red grape, kiwi fruit, pink grapefruit, white grape, banana, apple, tomato, pear, and honeydew melon. Since the anti-platelet activity in fruits is quite different from their antioxidant properties, it is possible that these activities are due to the presence of compounds that have a different chemical structure. Tomato extract used in a dose-dependent manner inhibited ADP-induced platelet aggregation; i.e., 25 µl of tomato extract (100% juice) inhibited platelet aggregation by 63% compared with the control whereas, 50 µl of tomato extract (100% juice) inhibited 75% of collagen-induced platelet aggregation in a 500 µl assay. The IC50 (minimum concentration required for 50% inhibition of platelet aggregation induced by ADP in 500µl PRP) of tomato extract was around 20µl (100% juice). The tomato and kiwifruit extract inhibited both collagen-and ADP-induced platelet aggregation to a similar extent but, could not inhibit arachidonic acid-induced aggregation and thromboxane synthesis.
Further characterisation of anti-platelet factors in tomato extract

Delipidation of the tomato ultrafiltrate (100,000 x g) obtained from the tomato extract demonstrated that the anti-platelet factor(s) were not lipid-soluble compounds. The delipidated aqueous fraction was further purified by gel filtration using a Bio gel P2 column (Figure-1). Among several peaks that emerged from the column, peaks- 3 and -4 showed high anti-platelet activity. Figure-2 shows the inhibitory effect of tomato extracts (peak-3 and peak-4) on whole blood aggregation induced by ADP. Peak–4, when subjected to HPLC using an anion ion exchange column, resolved into several peaks. Figure-2 shows the anti-platelet activity for peak 3 and peak-4 in whole blood aggregation. Maximum anti-platelet activity was associated with F2. However, the pooled fraction (F1) eluted prior to F2, also had some anti-platelet activity. Like peak-4 and peak-3, F2 had a similar inhibitory effect against ADP (79-87% inhibition) and collagen–induced platelet aggregation (60-97%) when incubated with PRP for 10 min. These tomato fractions inhibited TXB2 synthesis in response to ADP or collagen (almost 57-97% inhibition compared with the control) but, could not inhibit its synthesis when arachidonic acid was used. This indicates that the active components present in tomatoes inhibit platelet aggregation without involving the thromboxane pathways (the cyclooxygenase system). Since adenosine is a platelet inhibitor, the anti-platelet activity of tomato extract or tomato-derived components could be due to the presence of adenosine. In order to examine whether there were other components apart from adenosine responsible for inhibition of platelet function, samples of tomato extracts from peak-3, peak-4 and F2 were deaminated and then, their effect on platelet aggregation was determined (Figure-3). Adenosine deaminase, at a final concentration of 8U/ml, was effective at deaminating adenosine (4mg/ml), decreasing its effectiveness as an anti-platelet agent from 61% to 7% inhibition in ADP-induced platelet aggregation.
Figure 2. Effects of tomato extract on whole blood aggregation induced by collagen. Whole blood was incubated with peak-3 or peak-4 for 10 min. before collagen (1µM) was added to initiate aggregation. Control (- -), Peak-3 (- -), Peak-4 (- o -).

Figure 3. Effect of deaminated tomato extract on ADP-induced platelet aggregation where, A = Adenosine; DA = Deaminated Adenosine; P = Peak; DP = Deaminated Peak. Platelet aggregation response to ADP was measured after incubating 450 ml platelet rich plasma (PRP) with 20 ml of the tomato fractions and adenosine (with or without deamination). For details please see Duttaroy et al. 2001.

Deamination of adenosine was evident from the disappearance of an adenosine peak and appearance of inosine in our assays. The deaminated F2 sample showed a complete loss of adenosine and also anti-platelet activity whereas, deaminated peak-4 inhibited ADP-induced aggregation by 50% compared to 94% for the untreated peak-4 (p<0.01); the anti-platelet activity of peak-3 was unaffected by adenosine deaminase treatment under
similar experimental conditions. These data indicate that tomato juice contains antiplatelet compound (s) other than adenosine. When inhibition of thrombin-induced platelet aggregation by adenosine, aspirin and tomato extracts was examined, only tomato extract inhibited thrombin–induced platelet aggregation and this inhibition was as high as 99% in some cases.

These anti-platelet compounds in tomato, had a molecular mass less than 1000da, were highly water soluble and were stable after boiling. In addition to adenosine, tomato extract has other anti-platelet compounds (that were not destroyed by adenosine deaminase treatment, and that had anti-thrombin activity); however, their structure is yet to be determined. In addition to its anti-platelet property, adenosine modifies several important cellular processes in the cardiovascular system; i.e., it relaxes vascular smooth muscle, inhibits both the aggregation of platelets and the generation of superoxide anions by neutrophils and, prevents adhesion of neutrophils to the endothelium. Various physiological effects of adenosine act synergistically to maintain coronary blood flow and to attenuate myocardial injury due to ischemia and reperfusion. Tomato extract, by virtue of its adenosine content, may also synergistically inhibit thrombin-induced platelet aggregation by other inhibitors.

The thromboxane pathway does not appear to be involved in tomato extract inhibition of platelet aggregation. This is quite different than that of aspirin. Aspirin’s anti-platelet action involves inhibition of the cyclooxygenase enzyme in platelets, leading to decreased formation of prostaglandin G2, a precursor of TxA2 and thus, blocking the formation of TxA2, a platelet aggregation agonist. Since tomato extract or the fractions derived from it, do not inhibit the thromboxane pathway, it is possible that their mode of action is upstream of the platelet activation/aggregation processes but, not of thromboxane synthesis. Adenosine raises the level of cAMP in platelets; however, it does not inhibit thrombin-induced platelet aggregation by itself. The anti-platelet agents in tomatoes, however, may work as direct inhibitors of thrombin, as fibrinogen-receptor antagonists, or as specific inhibitors of collagen- and ADP-induced platelet aggregation. Further work using purified compounds isolated from tomato is required in order to understand which of the above steps are affected in the activation of platelets.

So, despite aspirin’s inhibition of TxA2, platelets may be induced to aggregate by other triggers such as thrombin – the most potent agonist of platelet aggregation. However, tomato-derived compounds also inhibit thrombin-induced platelet aggregation. Anti-thrombotic properties of tomato have been demonstrated in a rat model (Yamamoto et al. 2003). Recently, we completed two trials using tomato extracts in humans volunteers (O’Kennedy et al. 2006a; b). A significant reduction in platelet aggregation induced by both ADP and collagen was observed at 3h after consuming tomato extract (O’Kennedy et al. 2006a; b).

In conclusion, tomato extracts or derived products may equally be effective at inhibiting platelet aggregation induced by collagen, ADP and thrombin. Our data provides evidence that tomato extracts have great potential for increasing the effectiveness of thrombosis prophylaxis through an oral tomato extract therapy. Modulation of platelet reactivity towards collagen, ADP and thrombin by tomato extract could be of potentially prophylactic and therapeutic benefit in preventing and halting pathologic processes that lead to CVD.
References


