

Blood Thinning Effects and Phytonutrients

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INTRODUCTION

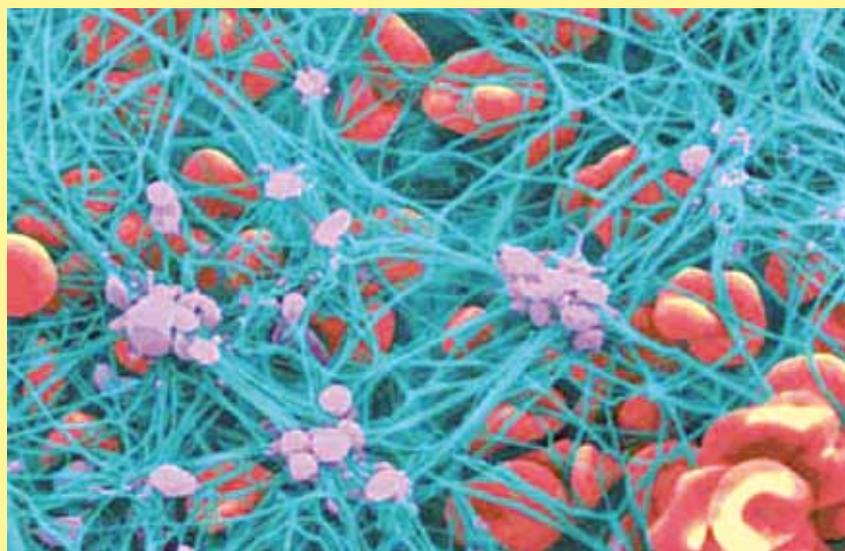
The cardiovascular system also known as the circulation system, involves the heart and all the blood vessels. These blood vessels can be referred to as the transport system of our body. They transport nutrients, oxygen, vitamins and minerals to the entire body and remove the waste materials. Hence, any damage or injury to the blood vessels must be repaired immediately. A disruption in the blood flow will deprive our body especially the heart of all the necessary nutrition. When there is an injury, natural response will take place in order to prevent excessive blood loss by forming blood clots to seal the injury. The process responsible for this purpose is platelet aggregation which is the clumping of platelets to form a thrombus (clot). Platelets are tiny components in the blood but they play a vital role in forming clots. The clot consists of tiny threads that trap the red blood cells and prevent them from leaking. This will stop bleeding and reduce blood loss (*Figure 1*). Platelet aggregation is a normal process in the body. However, unnecessary formation of blood clots will block the blood vessels and cause cardiovascular diseases such as heart attack and stroke.

in blood will attach themselves to the damaged blood vessels and clump together. Eventually, the fibrin threads (threads of the clot) will be formed to seal or cover the injury (*Figure 2*). This will prevent further blood loss. Vitamin K and calcium ions play an essential role in this cascade.

Platelet aggregation that leads to the formation of thrombus is vital in preventing excessive blood loss. However, abnormal clot formation or thrombosis is dangerous as it can cause serious medical conditions depending on the location it is formed. A clot in the

THE MECHANISM OF PLATELET AGGREGATION

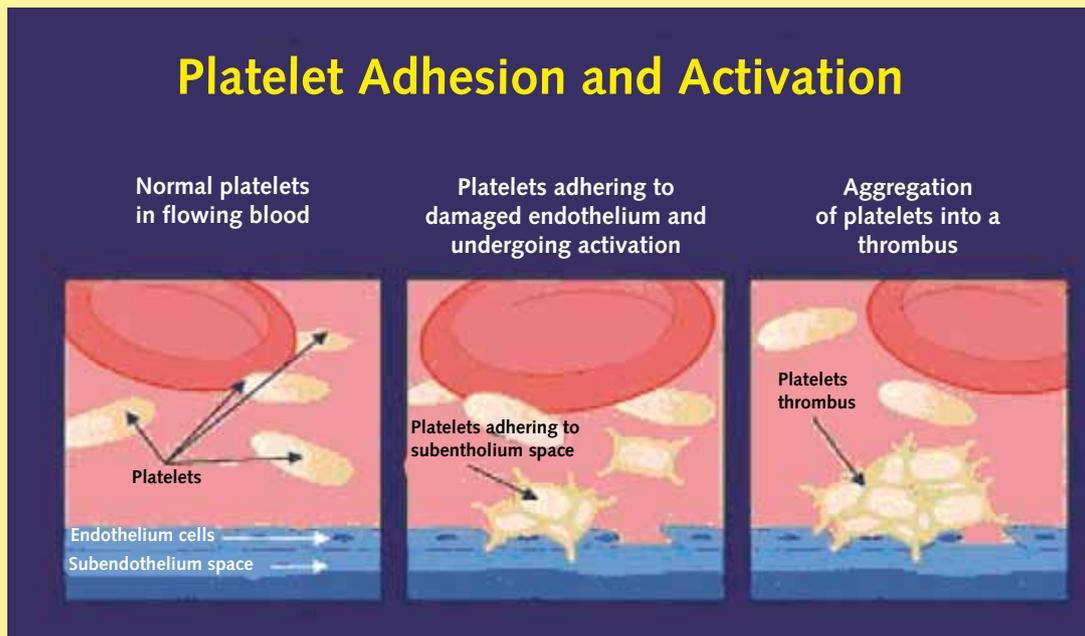
The clotting of blood involves a series of reaction known as the clotting or coagulation cascade. It is a complex enzymatic reaction involving clotting factors that are identified by Roman numerals. There are two pathways involved in platelet aggregation; the extrinsic and intrinsic pathways that will converge into the common pathway. Platelets that are normally present



Source: adapted from Veklich and Weisel (2008).

Figure 1. Blood clot visualized under colourized scanning electron microscope.

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Source: adapted from Ferguson (2000).

Figure 2. The steps involved in clot formation.

blood vessels that leads to the heart muscles may cause heart attack. Meanwhile, a clot in the vein causes deep vein thrombosis. Thus, 'blood thinners' or anti-coagulants are used to prevent unnecessary and extensive clot formation.

ANTI-COAGULANTS

Anti-coagulants prevent the formation of clots and they are prescribed to patients with coronary heart diseases. There are two types of anti-coagulants oral and intravenous.

Heparin

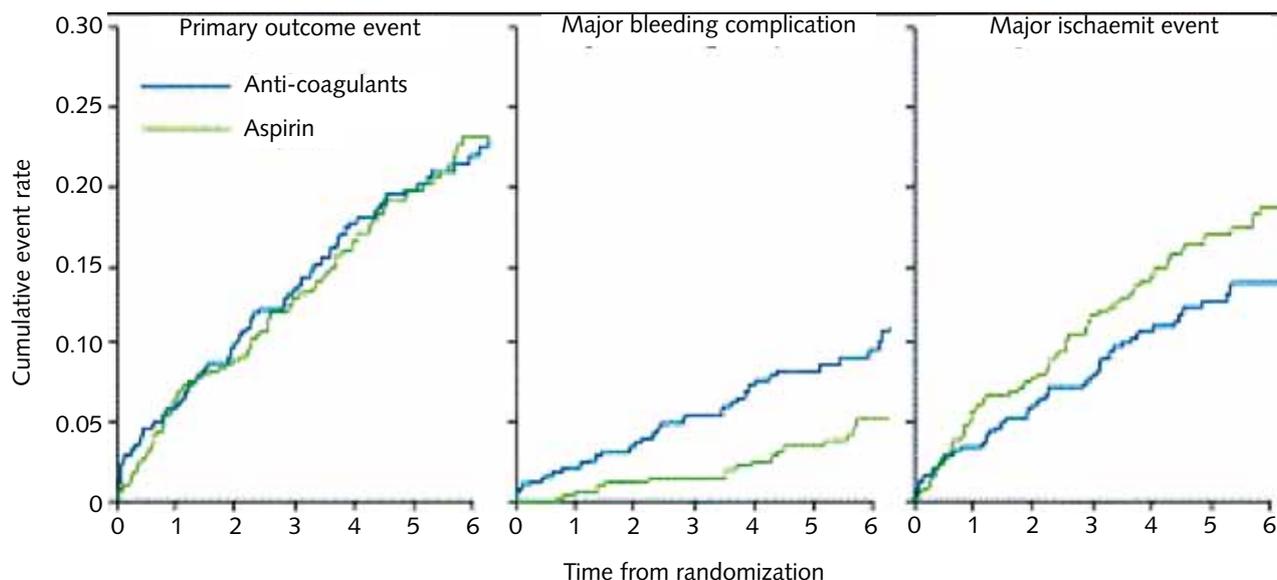
Heparin is an intravenous anti-coagulant with fast onset of action. However, heparin causes a few side effects such as osteoporosis, bleeding and thrombocytopenia (low number of platelets in blood). This compound is eliminated mainly by the kidney and therefore patients with severe kidney disease may face problems in excreting it (Vitin *et al.*, 2008).

Aspirin

Aspirin is an oral anti-coagulant effective in preventing heart diseases in high risk patients. Aspirin is the common name for acetylsalicylic acid that is abundant in plants such as the willow tree. Even Hippocrates, the father of medicine prescribed it for pain and fever. Research has proved its many therapeutic effects such as relieving fever and pain at low dosages. Its anti-coagulant effect is mainly through impairing platelet aggregation by inhibiting an enzyme, cyclooxygenase (COX) that produces pain, fever and coagulation as well as maintains the protective lining of the stomach (Ehmke *et al.*, 2002). Inhibition of this enzyme by aspirin will eventually lead to the prevention of clot formation (Undas *et al.*, 2007) (Figure 3). However, aspirin's side effects, which are stomach upset and excessive bleeding occurs because aspirin affects the protective lining of the stomach.

Warfarin

Warfarin is the frequently prescribed anti-coagulant. It inhibits an enzyme needed to replenish vitamin K that is needed for clot formation (LaSala *et al.*, 2008). However, several conditions such as the interaction of warfarin with other drugs and food, biological variation in response, delayed onset of action and the need for frequent laboratory monitoring are major concerns and drawback factors for warfarin prescription as they may cause excessive bleeding (Ansell *et al.*, 2004). On the other hand, genetic variation among individuals is a rising cause of concern. Mutations in the enzymes that interact with warfarin and clears it from the body reduce the enzymes' sensitivity and response to warfarin. Hence, patients are less susceptible to suppression by warfarin and require increased dosage. Based on a study, these mutations are the reason behind African American's resistance and Asian American's in-



Source: adapted from Algra (2007).

Figure 3. Effect of aspirin compared to other oral anti-coagulants.

creased sensitivity to warfarin (La-Sala *et al.*, 2008).

NATURAL PRODUCTS WITH ANTI-THROMBOTIC ACTIVITIES

Natural foods are also being investigated for their inhibitory activity on platelet aggregation. Among these are grapes and their fermentation products such as red wine. Studies have shown that grapes are able to inhibit platelet aggregation *in vitro* and thrombus formation *in vivo*. A possible mechanism for this activity may be attributed to the antioxidant activity of grapes. Moreover, proanthocyanidin, a compound purified from grape seeds further increased the anti-platelet and anti-thrombotic activity (Sano *et al.*, 2005). Another similar study conducted using a compound found in grape skins; resveratrol is also known to reduce platelet aggregation in a similar way as aspirin (Das *et al.*, 2010).

In addition, turmeric, a well-known spice has also shown anti-thrombotic effect (Shah *et al.*, 1999). Studies have found that the compound responsible for this activity is curcumin. Curcumin has inhibitory activity on thromboxane, similar to aspirin (Srivastava *et al.*, 1995).

On the other hand, olive oil also inhibits platelet aggregation. Olive oil consists of monounsaturated fatty acids and polyphenols that contribute to human health. The phenolic fraction of olive oil is able to inhibit platelet function *in vitro*. The decrease in platelet function further reduced their ability to aggregate and form clots (Petroni *et al.*, 1995). Similar to olive oil, salmon oil was also found to reduce platelet aggregation. Nine healthy men were fed with salmon oil which is the source of dietary n-3 fatty acids. The results revealed that salmon oil not only decreased

platelet sensitivity to ADP (platelet activator) but also decreased the platelet count (Nelson *et al.*, 1991).

PALM OIL - A NATURAL SUBSTITUTE

Due to the rising concern for the safety of patients under anti-coagulation prescription, many studies have been carried out to develop new oral anti-coagulants. Vitamin E has gained much attention due to its active compounds namely tocopherols and tocotrienols. Both compounds exist in four isomers (alpha, beta, delta and gamma). Thus, palm oil that is rich in vitamin E exhibits various protective activities. The γ -tocotrienol is found in abundance in palm oil followed by α -tocopherol, α -tocotrienols and δ -tocotrienols. Tocopherols are mainly found in corn, soyabean and olive oil while tocotrienols are found in large quantities in palm oil, rice bran and barley oil. Both

tocopherols and tocotrienols share similar chemical structure except that tocotrienols consist of unsaturated side chain. This property allows tocotrienols to easily pass through the lipid bi-layer compared to the saturated tocopherols and contributes to many protective mechanisms in the body (Sambanthamurthi *et al.*, 2000). Previous studies have shown that α -tocopherol alone does not inhibit platelet aggregation but enhances the inhibitory effect of other compounds. The lack of a proper mechanism in decreasing platelet aggregation by tocopherols turned the attention towards tocotrienols (Sen *et al.*, 2006).

TOCOTRIENOLS AND ANTI-THROMBOTIC EFFECTS

Many studies have shown that tocotrienols lower serum cholesterol levels and suppress platelet aggregation *in vitro* (Mutalib *et al.*, 2003). It has also shown anti-proliferative effects on breast cancer cells (Nesaretnam *et al.*, 2004). Theriault *et al.* (1999) reported that intake of tocotrienol-rich fraction (TRF) inhibits platelet aggregation by reducing the synthesis of thromboxane (a platelet activator). This mechanism is similar to the anti-coagulative effect of aspirin.

A study by Aggarwal *et al.* (2010) also showed that tocotrienols have cardio-protective effects. Intake of palm oil have shown an increase in clotting time and therefore reduced platelet aggregation by reducing the amount of fibrinogen (a compound that initiates the formation of the fibrin threads to seal the wound) (Pereira *et al.*, 1991). Therefore, they may serve as an anti-coagulant or anti-

thrombotic agent replacing aspirin and warfarin in future.

CONCLUSION

Platelet aggregation is a complex enzymatic process that involves many factors. In a normal physiological condition, aggregation of platelets leads to the formation of clots that help to prevent excessive blood loss. However, uncontrolled or abnormal formation of clots may cause serious health disorders especially in patients with cardiovascular diseases. Although many studies have revealed the potential of natural compounds especially tocotrienols in palm oil to inhibit platelet aggregation, more conclusive studies looking at the interaction between other food and dosages should be carried out. These studies should also include clinical trials to test the efficiency of the dosages of tocotrienols in order to achieve the best results. This would ensure the safety of these compounds to serve as an anti-thrombotic agent.

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