# Fruitflow® as Dietary Antiplatelets

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Fruitflow® is derived from ripe tomatoes using a process that removes pomace, seeds, and fats while operating at low processing temperatures (~40 °C) to control the production of artefacts such as Maillard/Amadori products or Strecker aldehydes. Fruitflow® is standardised regarding representatives of its three main classes of antiplatelet compounds—nucleosides, phenolic derivatives, and flavonoid derivatives—and the total amount of 'bioactive extract' present.

Keywords: platelet function ; platelet activation ; inflammation ; immunothrombosis ; particulate air pollution ; dietary antiplatelet ; water-soluble tomato extract

## 1. Introduction

Platelets play a key role in maintaining homeostasis of the blood and preserving the integrity of the vascular system. These anuclear cell fragments possess a varied range of cell surface receptors and produce many signalling molecules released on activation [1]. Their ability to respond to a diverse array of external stimuli renders them exquisitely sensitive to any stresses experienced by the vascular system. However, this sensitivity can also result in a hyperaggregable state, where a proportion of circulating platelets are chronically sensitised by their environment—the blood and vascular endothelium—and can contribute to pathologic processes [1][2].

While antiplatelet medications are appropriate for the treatment of illness or control of disease, they are unsuitable in the context of primary prevention. Antiplatelet drugs—for example, acetylsalicylic acid, dipyramidole, and abciximab—typically act on a particular pathway of platelet aggregation, which, as a result, is completely suppressed. This level of platelet suppression is linked to increased bleeding tendencies, to the extent that risk from bleeding outweighs the antiplatelet benefits. Nutritional approaches to lowering platelet hyperactivity are attractive, and quite a range of plant-derived antiplatelets are known, including pycnogenol from pine bark [3], sulfur derivatives from garlic [4], flavonoids from onion, grapes and olive oil, and berry anthocyanidins are some of the most well studied [5].

## 2. The Active Components, Mechanisms of Action, Efficacy and Safety of Fruitflow®

Fruitflow® is a lycopene-free water-soluble extract with a compositional profile as close to fresh clarified tomato juice as practical. It is further processed to remove both polysaccharides and soluble sugars, which comprise most of its dry matter content but does not contribute to its antiplatelet activity. The resulting powder contains a range of nucleotides and nucleosides (including adenosine, cytidine, guanosine, AMP, GMP, and deoxy derivatives), a range of simple phenolic compounds (e.g., caffeic and ferulic acids, glycosides, and conjugates with quinic acid) and a range of flavonoid derivatives in which quercetin derivatives dominate. The processing conditions are controlled to prevent degradation of glycosides and other derivatives, and to retain a compositional profile close to that of fresh tomato juice. Fruitflow® is standardised regarding representatives of its three main classes of antiplatelet compounds—nucleosides, phenolic derivatives, and flavonoid derivatives—and the total amount of 'bioactive extract' present. It is also standardised by bioassay, measuring its IC50 in preventing platelet aggregation in response to ADP, collagen, arachidonic acid, and thrombin. The production of a standardised extract that can be consumed in small amounts has facilitated research into the antiplatelet effects of tomato compounds, avoiding the variability inherent in using juices or other food formats.

Fruitflow® does not directly affect blood coagulation at any dose tested. Antiplatelet effects were placed into clinical context by comparing the effects of Fruitflow® with those of 75 mg aspirin; in this study, it was shown that Fruitflow affects platelets approximately one third as strong as aspirin and does not dangerously elevate the bleeding time in the manner that aspirin does [6]. The lower strength of its effects on the haemostatic system, compared with aspirin, can be linked to the fact that Fruitflow does not have a cumulative effect when consumed daily, unlike aspirin [6]. Thus, the efficacy and safety profile of Fruitflow® are suited to use in primary prevention, whereas aspirin is not.

## 3. Dietary Antiplatelets in Inflammation

### 3.1. Exercise-Induced Inflammation

Strenuous exercise is associated with an increased risk of vascular thrombotic events and sudden death [7]. We experience stress related to exercise as lack of breath, muscular fatigue, or even acute pain. On a molecular level, during exercise, we are inducing an inflammatory burst, which is mediated by platelets. Strenuous exercise releases adrenalin and serotonin and generates thrombin [8], resulting in platelet activation [7].

The second consequence of platelet activation during exercise is increased inflammation, manifesting as increased circulating IL-6, increased circulating microparticles, and leukocyte and reactive oxygen species (ROS) accumulation in muscle after exercise. These parameters are linked to longer recovery times [9]. Typical signs of this are delayed muscle soreness, muscle damage due to poor recovery, and difficulty adhering to a training regime.

Fruitflow® can reduce TF binding to P-selectin, thus reducing platelet-generated thrombin release. Fruitflow® also directly reduces the platelet response to circulating thrombin. To examine the likely effect of a dietary antiplatelet in this area, we conducted preliminary experiments to examine the in vitro effects of Fruitflow® on thrombin- and epinephrine-stimulated platelets and on human umbilical cord endothelial cells (HUVEC) stimulated by activated platelet-leukocyte suspension. Treatment of HUVEC cells with Fruitflow® prior to stimulation reduced platelet aggregation and microparticle formation (index of platelet activation) by 91% and 31%, respectively, compared with control. Fruitflow® treatment reduced IL-6 generation by stimulated HUVEC cells by approximately 80%, compared with non-stimulated control [10]. Thus mechanistically, it appears that Fruitflow, or another dietary antiplatelet affecting thrombin generation, has potential as an intervention in exercise-mediated hypercoagulability and the inflammation arising.

### 3.2. Air Pollution

Fruitflow® exerts some of its antiplatelet effects through mechanisms involving suppression of P-selectin and concomitant suppression of TF binding to the platelet. It also reduces platelet microparticle formation [11]. Since both mechanisms are implicated in platelet activation by air pollution, we conducted some exploratory tests to expose platelets to airborne particulate matter, such as diesel emissions, in the presence or absence of Fruitflow®. These in vitro tests showed that Fruitflow® reduces the platelet activation caused by $PM_{2.5}$ by approximately one third [12]. Our early work showed that the phenolic glycosides contained in Fruitflow® are strongly linked with their effects on thrombin-mediated platelet activation; we hypothesise that compounds such as chlorogenic acid and other caffeic acid glycosides, as well as ester derivatives of phenolic acids, are important in mediating these effects. Other dietary antiplatelets, such as phenolic fractions from olive oil, or onions, may also be of interest if standardized extracts become available.

## 4. Summary

Platelets have multifaceted functions which generate a complicated set of interactions with other vascular cells, leading to many roles outside haemostasis. As our understanding of the role of platelet activation in response to— and in complicating—inflammatory and infectious illnesses grow, it becomes more apparent that platelet-targeted treatments are necessary outside the field of CVD. Dietary antiplatelets such as Fruitflow® can help provide suitably gentle and safe yet efficacious treatments to improve public health in response to a wide range of health challenges.

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