Dietary antiplatelets: a new perspective on the health benefits of the water-soluble tomato concentrate Fruitflow®

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Abstract: Understanding platelet functionality has undergone a sea change in the last decade. No longer are platelets viewed simply as regulators of haemostasis; they are now acknowledged to be pivotal in coordinating the inflammatory and immune responses. This expanded role for platelets brings new opportunities for controlling a range of health conditions, targeting platelet activation and their interactions with other vascular cells. Antiplatelet drugs may be of wider utility than ever expected but often cause too strong a platelet suppression to be used out of clinical settings. Dietary antiplatelets represent a nutritional approach that can be efficacious while safe for general use. Here we review potential new uses for dietary antiplatelets outside the field of cardiovascular health, with specific reference to the water-soluble tomato extract Fruitflow®. Uses in different aspects of inflammation and immune function are discussed, highlighting exercise-induced inflammation, mediating the effects of air pollution, and controlling thrombotic aspects of the immune response. Potential future developments in women’s health, erectile dysfunction, and the allergic response give an indication of how wide-ranging the utility of dietary antiplatelets can possibly be.

Keywords: Platelet function, platelet activation, platelet hyperactivity, platelet-leukocyte aggregates, 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 signaling 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 becomes chronically sensitised by their environment – the blood and vascular endothelium – and in this situation, platelets can contribute to pathologic processes[1, 2]. The most widely studied example is platelet influence on the development and progression of cardiovascular disease (CVD); antiplatelet therapy has been a cornerstone of treatment for established CVD for many years. Platelets are also involved in immune responses and host defences, and recent work has suggested that the haemostatic and immune systems are intimately linked rather than separate entities[3]. With the growing recognition of the critical role of platelets in inflammation and immune responses[4], it has become evident that control of platelet-driven inflammatory responses in many diseases other than CVD is important. Recent studies have indicated that antiplatelet medications may reduce mortality from infections and sepsis[5].
The water-soluble tomato extract known as Fruitflow® is a dietary antiplatelet. Fruitflow® contains a range of tomato-derived secondary metabolites, including nucleosides, phenolic conjugates and polyphenols, all of which show different profiles of antiplatelet activity[6]. When consumed daily, Fruitflow® reduces platelet aggregation in response to major platelet agonists - adenosine diphosphate (ADP), collagen, arachidonic acid, and thrombin[6, 7]. A range of human studies in healthy subjects has established an average reduction in platelet aggregation of 9 – 23%, depending on the agonist used[6-10]. In Europe, this has been judged suitable for use in primary prevention, with the aim of preventing platelet hyperactivity, and a specific health claim has been granted: Fruitflow® helps maintain normal platelet aggregation which contributes to healthy blood flow[11].

We have previously summarised the body of work related to Fruitflow®'s effects on platelet aggregation, most of which have been carried out in the context of cardiovascular health[12]. This review focuses on potential new uses for a dietary antiplatelet such as Fruitflow® in the areas of inflammation and immune function and suggests other potential targets for future research into the health benefits of dietary antiplatelets.

2. Overview of the active components and mechanisms of action of Fruitflow®

As the composition, preparation, and antiplatelet effects of Fruitflow® have been reported elsewhere[6, 12-19], we include here a brief description of the ingredient and its main mechanisms of action. Fruitflow® is derived from ripe tomatoes, by a process which 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. It is thus 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 make up most of its dry matter content but do not contribute to its antiplatelet activity, and dried. 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, again to retain a compositional profile close to that of fresh tomato juice. Fruitflow® is standardised with regard to representatives of its three main classes of antiplatelet compounds, that is nucleosides, phenolic derivatives and flavonoid derivatives, and the total amount of ‘bioactive extract’ present. It is also standardised by bioassay, by measuring its IC50 in preventing platelet aggregation in response to ADP, collagen, arachidonic acid and thrombin. The production of a standardised extract which 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.

Proteomic experiments carried out to examine effects of Fruitflow® on platelet signaling pathways have shown that those regulating platelet structure, coagulation, and redox status are strongly affected. The downstream effects of changes to these signaling pathways are observed in reduced activation of integrin αIIbβ3 (GPIIb/IIIa), an activation step common to multiple aggregation pathways, as well as lower induction of P-selectin (CD62P) on the platelet surface, and lower binding of circulating tissue factor (TF). These changes functionally alter platelet capacity to form stable aggregates and to activate thrombin generation. Effects on protein disulphide isomerase (PDI), an oxidoreductase which catalyses the formation and the isomerisation of disulfide bonds, may underly many of these changes to platelet function and can be linked specifically to quercetin derivatives present. In platelets, blocking PDI with inhibitory antibodies inhibits several platelet activation pathways, including aggregation, secretion, and fibrinogen binding.
3. Dietary antiplatelets in inflammation

Platelets release a plethora of inflammatory mediators with no known role in haemostasis. Many of these mediators modify leukocyte and endothelial responses to a range of different inflammatory stimuli[20]. Platelet-leukocyte aggregates are now regarded as a key aspect of the inflammatory response, bridges between leukocytes and endothelium, which are largely mediated by platelet P-selectin[20, 21]. Platelets have emerged as crucial coordinators of inflammation through their interactions with monocytes, neutrophils, lymphocytes, and the endothelium. As a response to injury or disease, the versatility and reactivity of platelets in recruiting leukocytes and initiating an inflammatory response are highly beneficial. However, the reactivity of platelets also brings disadvantages, sometimes generating and maintaining a raised inflammatory burden which accelerates tissue damage or the progress of a disease, for example in atherosclerosis, diabetes, or inflammatory bowel disease[22-24]. In such conditions, use of antiplatelet therapy is common to restrict platelet hyperactivation, and control inflammation.

Dietary antiplatelets come into play under circumstances where persistent platelet activation arises in response to dietary and lifestyle factors – notably smoking or exposure to smoke / air pollution, consistently high levels of plasma glucose, and certain exercise patterns. Some degree of platelet hyperactivity is common among apparently healthy subjects, and while this does not constitute a ‘health condition’ in itself, it results in interactions that increase the release of IL-6 and NFkB[20], increases the levels of circulating microparticles (most of which are platelet-derived)[25], increases thrombotic tendencies[26], and raise CRP levels[4, 27]. The increased inflammatory burden can hinder the body’s response to external stresses and lower general resilience, as well as predisposing early development of conditions such as diabetes or atherosclerosis over time. Dietary antiplatelets have a clear role to play in modifying the platelet response to a pro-inflammatory environment in the vascular system when it is unsuitable to use antiplatelet drugs for this purpose. Two specific instances illustrating such usage will now be discussed.

3.1. Exercise-induced inflammation

The premise that there may be benefits from or even requirements for, antiplatelet action during exercise is often met with surprise. Exercise is associated with good health, and increasing exercise is usually linked to longer life, better mental health, less metabolic problems, stronger bones, and improved cardiovascular health[28]. However, strenuous exercise is associated with an increased risk of vascular thrombotic events and sudden death[29]. 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[30], resulting in platelet activation[29]. In addition, intense aerobic exercise can reduce the amount of anti-aggregatory nitric oxide (NO) produced by the vascular endothelium, especially in untrained subjects, as the amount of oxygen reaching the NO-producing cells is reduced[31]. Hyperaggregability develops, and platelets then coordinate a series of pro-inflammatory events as described previously[32]. This sequence of events has two significant consequences. Firstly, after exercise, the potential for blood to coagulate to make a blood clot is increased. This is termed hypercoagulability, and this state can last for up to 48 hours after an exercise session[33]. The extent of hypercoagulability depends on the duration and intensity of the exercise undertaken, as well as training status – it is worse in untrained individuals at lower intensities of exercise but still occurs in well-trained individuals at higher intensities of exercise. This increase in coagulation capacity can be dangerous, especially for those with
underlying health conditions such as atherosclerosis or cardiac problems, leading to increased risk of thrombosis and sometimes even to sudden death[34]. It has been estimated that physically inactive individuals have about a 50-fold increase in the risk of sudden death and a 100-fold increase in the risk of a heart attack when they perform vigorous exercise[35]. These risk levels can be substantially reduced by regular physical training, but an association with vigorous exercise remains (risk raised two- to five-fold in athletes). Approximately 70% of exercise-induced sudden deaths and heart attacks in the over-35 age group are attributed to obstruction of arteries by platelet clots[35].

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[36]. Typical signs of this are delayed muscle soreness, muscle damage due to poor recovery, and difficulties in adhering to a training regime.

Many studies have examined the potential for nutritional interventions to reduce the inflammatory markers mentioned above after exercise, but results are generally inconsistent. Most of the interventions used primarily target either IL-6 or ROS[37, 38]. To examine the likely effect of a dietary antiplatelet in this area, we first examined 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 (Figure 1). Treatment of HUVEC cells with Fruitflow® prior to stimulation reduced platelet aggregation and microparticle formation by 91% and 31%, respectively, compared to control. Fruitflow® treatment reduced IL-6 generation by stimulated HUVEC cells by approximately 80% (compared to non-stimulated control)[39].

![Figure 1](image-url)

Figure 1. Effects of Fruitflow® on platelet and HUVEC responses to thrombin and epinephrine in vitro. A: Platelet aggregation measured by light transmission aggregometry in platelet-rich plasma in response to thrombin receptor analogue peptide (TRAP) and epinephrine, after prior incubation with either control or Fruitflow®. Data is shown as the area under the aggregation curve. B: Increase from baseline platelet microparticle count after stimulation of platelet suspension with TRAP and epinephrine. Data are shown as % change from baseline count. C: IL-6 expression from HUVEC cells exposed to activated platelet-leukocyte suspensions or control in the presence or absence of Fruitflow®. Con- represents control HUVEC cells not treated with activated platelet-leukocyte suspension. Con+ represents HUVEC cells treated with platelet-leukocyte suspension and saline (control). Fruitflow® represents HUVEC cells treated with platelet-leukocyte suspension and Fruitflow®. Data are shown as pg/ml IL-6.
A small exploratory study using a treadmill test in 6 untrained men aged 18 – 55 showed that exercising for 20 minutes at 70% VO\textsubscript{2max}, followed by exercising at 90% VO\textsubscript{2max} until self-determined exhaustion, resulted in post-exercise increases in markers of platelet activation, coagulation, and inflammation (Table 1). Consuming Fruitflow® 90 minutes prior to exercise led to decreased systemic activation compared to a placebo supplement. Exercise-induced platelet microparticle generation was reduced by 77% compared to control, and the induced increase in thrombin generation capacity was reduced by 89%. The reduced haemostatic system activation was accompanied by decreased circulating IL-6, which was 58% lower post-exercise after consuming Fruitflow® than after consuming a placebo.

Table 1. Post-treadmill exercise effects on platelet activation, coagulation and inflammation in men aged 18-55 (n = 6).

<table>
<thead>
<tr>
<th></th>
<th>Plasma microparticle count(^1)</th>
<th>Plasma thrombin generation capacity(^2)</th>
<th>Circulating IL-6(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo treatment (n=6)</td>
<td>93</td>
<td>120</td>
<td>345</td>
</tr>
<tr>
<td>Fruitflow® treatment (n = 6)</td>
<td>21</td>
<td>13</td>
<td>145</td>
</tr>
</tbody>
</table>

\(^1\) Plasma microparticle count is a measure of platelet aggregability, measured by flow cytometry.

\(^2\) Plasma thrombin generation capacity is a measure of coagulation and is measured by a fluorescence-based assay in which the evolution of thrombin is monitored over time.

\(^3\) IL-6 was measured by ELISA.

The work discussed here is preliminary only and needs to be interrogated in much larger studies. It remains to be seen whether reducing induced inflammation can significantly impact on subsequent muscle soreness, and exercise frequency, thus enabling a healthier and fitter lifestyle, especially important with increasing age. However, these exploratory experiments serve as an interesting suggestion that potentially, dietary antiplatelets could be of utility in reducing exercise-induced inflammation where antioxidants have not proven efficacious.

3.2. Air pollution

The great majority of the world’s population (92%) now breathe air that does not meet World Health Organization guidelines. As reported by the Global Burden of Disease Report, outdoor fine particulate matter (particulate matter with an aerodynamic diameter < 2.5 \(\mu\)m) exposure is the fifth leading risk factor for death in the world, accounting for 4.2 million deaths [40]. The World Health Organization attributes 3.8 million additional deaths to indoor air pollution. As such, air pollution is now the largest environmental risk factor for ill health. Pollutants in the air come from a range of sources, and are defined as primary pollutants if released directly from industrial or transportational activities (e.g. sulfur and nitrogen oxides and carbon monoxide), or as secondary pollutants if they form in the atmosphere from / by interacting with the primary pollutants (e.g., ozone, particulates). Arguably the most toxic form of air pollution is particulate matter (PM).

Particulate air pollution is related to both natural events - volcanic emissions, dust storms, forest fires - and human activities such as vehicle or machinery emissions and traditional cooking practices. Both types of event result in the suspension of soot, gases and other matter in the air as tiny particles (PM). PM is usually classified by its size; PM\(_{10}\) denotes particles < 10 \(\mu\)m in diameter; PM\(_{2.5}\) particles are < 2.5 \(\mu\)m in diameter; and PM\(_{0.1}\) particles are < 0.1 \(\mu\)m in diameter. Smaller PM are more toxic than larger, as they are easily transported to more tissues in the body. PM\(_{2.5}\) is small enough to penetrate lung
alveoli, and while PM0.1 passes through the alveolar-capillary membrane and into the bloodstream[40]. PM in the bloodstream induces cytotoxic and inflammatory responses, and there is a recognised link between exposure to diesel emissions and cardiovascular disease[41]. Particulate matter has been shown to promote arterial thrombosis and atherosclerosis through increased platelet activation[42], leading to accelerated coronary heart disease and strokes, which are the main causes of death from air pollution[40, 41].

In a 2018 review of the impact of air pollution on thrombosis, Robertson et al concluded that acute exposure to PM2.5 shifts the haemostatic balance towards a pro-thrombotic/pro-coagulative state[42]. Platelet activation and oxidative stress again result in the formation of platelet-leukocyte conjugates and increase in circulating IL-6. The interactions between platelets and TF appear to be relevant to activation in these conditions. A role for circulating platelet and leukocyte derived microparticles is also beginning to emerge[43]. With the chronic nature of exposure to air pollution, epigenetic changes are likely, leading to the development of heritable pro-thrombotic genotypes[44].

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[12]. As both mechanisms are implicated in platelet activation by air pollution, we carried out some exploratory tests to expose platelets to airborne particulate matter, such as that from diesel emissions, in the presence or absence of Fruitflow®. These in vitro tests showed that Fruitflow® reduces the platelet activation caused by PM2.5, by approximately one third (Figure 2)[45].

Figure 2. Effect of Fruitflow® on platelet aggregation induced by air pollution particulate matter. Platelet-rich plasma was treated with diesel particulate matter (50 µg/mL) in the presence or absence of Fruitflow®. Platelet aggregation was initiated with ADP agonist (2.5 µmolL⁻¹) and monitored on by light transmission aggregometry for 10 min at 37°C under stirring conditions. All tests were carried out in triplicate. Values are shown as mean ± SD.

As yet, there is no coherent body of work examining the effects of nutrition on the damage caused by air pollution. Whyand et al. conclude that while some nutritional components may be associated with some benefits (e.g., Vitamin D, Vitamin E, carotenoids, omega-3 oils, and the Mediterranean diet), is very little direct evidence of specific protective effects and that studies are needed urgently[46]. We suggest that dietary antiplatelets could form an interesting topic of investigation. Protecting platelets from the toxic effects of PM2.5 and PM0.1 may help to reduce the inflammatory burden, which develops and worsens over time.

4. Dietary antiplatelets in immunity
As we have discussed previously, platelets interact with circulating leukocytes in response to inflammatory stimulus primarily by inducing surface expression of P-selectin - or the surface glycoprotein, CD40, which bind to leukocyte PSGL1 and CD154 (CD40L), respectively, leading to the formation of platelet–leukocyte aggregates[20]. When these aggregates are formed with circulating monocytes or neutrophils, as well as triggering an inflammatory response, the innate immune response is triggered[4]. Interactions of platelets with the innate and adaptive immune responses have been one of the foremost areas of research in platelet biology in recent years, and it is now well established that platelets have a pivotal role in initiating and modifying the immune response[47-49]. Platelets contain the mRNA transcripts for all TLR1 to TLR10 (Toll-like receptors). These molecular pattern recognition receptors are key regulators in the initiation of the innate immune response to foreign organisms[50, 51]. Platelet-mediated CD40-CD154 interactions take place not only with leukocytes but also with dendritic cells, leading them to present antigen to T cells[4]. In addition, platelet activation can also lead to the release of δ-granule content and secretion of molecules such as serotonin and RANTES (regulated on activation, normal T cell expressed and secreted; CCL5) that are also known to mediate T-cell activation and differentiation. Platelets are known to directly recognize and internalize pathogens[52], and to modulate leukocyte behavior, enhancing their ability to phagocytose and kill pathogens[53]. Platelets are also involved in coordination of the production of Neutrophil Extracellular Traps (NETs)[54]. During certain stages of infection, platelet-initiated activation of both innate and adaptive immunity is beneficial to the host. When tissue damage is caused by blood-borne pathogens (viral or bacterial), the multifaceted platelet response involving multiple cellular interactions and secretions results in a coordinated intravascular coagulation response termed immunothrombosis[55]. During this process, platelets and immune cells form a physical barrier of confinement preventing dissemination of pathogens. However, uncontrolled endothelial damage and inflammation resulting from infection progression can lead to adverse prothrombotic responses and increased cardiovascular risk[55]. As an example, a thrombotic disease often associated with infection is sepsis, which leads to disseminated intravascular coagulation (DIC). DIC is characterized by microthrombus formation, blocking the microvasculature and causing widespread tissue / organ damage. A further example is the enhanced immunothrombosis that forms a characteristic of severe cases of COVID-19 disease, caused by the SARS-nCoV-2 virus. Severe infections with SARS-nCoV-2 can result in cytokine storm, systemic inflammatory response and immunothrombosis, leading to microvascular thrombosis (widespread blood clots in tiny blood vessels)[56]. Antiplatelet therapy has often been used in cases of severe infection, and even in some cases of less severe infection (e.g., use of acetylsalicylic acid in influenza). However, its use has become much more widespread since the advent of the SARS-nCoV-2 virus. Strong antiplatelet treatment is neither practical nor suitable for most COVID-19 patients who contract a mild / medium severity illness. However, targeting platelet hyperactivity may help to prevent or delay the progression of the illness from mild to more serious. The studies recently published by Manne et al.[57] and Hottz et al.[58] showed that production of TF (and by extension, thrombin) was blocked in COVID-19 illness by targeting the platelet. This was achieved by pretreating COVID-19 patient platelets with an anti-P-selectin neutralizing antibody or the clinically approved anti-αIIb/β3 monoclonal antibody, abciximab. The enhanced role of antiplatelets in managing COVID-19 has raised interest in nutritional interventions which might help to manage the progress of this, and similar, infections. The potential for nutritional status to impact on the progress of thrombotic complications in COVID-19 infection was reviewed in 2020 by Tsoupras et al[59]. This article concluded that nutrients with antithrombotic properties could benefit individuals infected by the Sars-CoV2 virus.
The underlying platelet hyperactivity associated with conditions such as diabetes and heart disease, or found in areas of high pollution, is significant, and the importance of tackling this has been laid bare by the consequent higher risk of thrombosis observed in COVID-19 infection. We suggest that a dietary antiplatelet like Fruitflow® could be considered for daily use, especially in those known to have a higher risk profile for complications during serious infection, that is, individuals who may be overweight, have high blood pressure, high blood sugars, or atherosclerosis, as well as all over 50s[60]. Fruitflow® could help reduce the platelet hyperactivity which forms a bridge between immune response to infection, and development of thrombotic complications. Intervention with a dietary antiplatelet is unlikely to be sufficient to overturn serious thrombotic complications such as those observed in sepsis or in severe COVID-19, and we are not advocating it for use in such conditions. Rather, we suggest that Fruitflow® may be of use to help improve the resilience of our bodies’ reaction to initial or mild infection, through its beneficial effects on blood platelets and thrombosis. The safety and suitability of Fruitflow® as a dietary antiplatelet are an important aspect of this suggestion, as its safety profile and relatively mild action make it useable by all normally healthy adults[60]. Immunity and resilience to viral infection is a focus area taking centre stage in the public consciousness worldwide. There is a clear drive from the public to find ways of boosting resilience and staying healthy in the face of infectious diseases, and it is imperative that the potential role of nutrition or dietary supplements is investigated.

5. Emerging areas of interest for dietary antiplatelets

5.1. Platelet hyperactivity during menopause

A growing focus on the menopause, and the changes in women’s cardiovascular health that accompany the reduction in oestrogen levels during menopause, has highlighted platelet hyperactivity as a target in this area. From puberty onwards, oestrogens play an integral role in female life. Apart from governing the reproductive system, they affect mood, appetite and energy. They also confer an enviable protection on the cardiovascular system, so that women’s risk of CVD is significantly lower than men’s, for 50 – 60 years[61]. When natural levels of oestrogens decline during perimenopause, this protective effect is lost. In the space of 5 – 10 years, women’s CVD risk rises to equal men’s[62].

In part, this effect relates to loss of oestrogen signalling to regulate the elasticity of blood vessels – oestrogens help to regulate this dynamic behaviour by signalling for the release of NO in the blood vessels, making them dilate[63]. The vasoconstricting effect of the menopausal drop in oestrogens is compounded by age-related reduction in NO. Oestrogens also directly affect control of platelet activation in women via platelet oestrogen receptors, which have an anti-aggregant effect when oestrogen is bound. This extra platelet control contributes to reducing women’s cardiovascular risk while oestrogen levels are high[64]. During perimenopause, platelet oestrogen receptors reduce in number, and after menopause, they disappear. Alongside reduced nitric oxide, this removes a layer of protection from women’s platelets. At the same time, the dropping oestrogen levels cause increased instability from disturbed metabolism, an unhealthy balance of blood fats, and damaged blood vessels. Platelets can become persistently sticky after menopause, both a cause and a consequence of women’s increased cardiovascular risk profile.

Reducing platelet hyperactivity during and after menopause may go some way towards compensating for the loss of the protective effects of oestrogen on the cardiovascular system. Alongside diet and exercise advice, and HRT where appropriate, dietary antiplatelets appear a potentially useful adjunct therapy suitable for long term use.
5.2. Erectile dysfunction

Another major consequence of low NO levels and the associated increased platelet hyperactivity manifests in men, as erectile dysfunction (ED), a disorder with widespread prevalence[65]. The successful use of Sildenafil in ED highlighted the central role played by nitric oxide (NO) in mediating normal erection and in the pathogenesis of ED[66]. Platelet hyperactivity is thought to contribute to countering erection through release of vasoconstrictors, superoxide and other oxygen free radicals[67]. Low NO facilitates the adhesion of platelets and leukocytes to vascular tissue via P-selectin and GPIIbIIIa. The adhered platelets then release vasoconstrictors, hindering erection.

Some researchers consider that ED may be a manifestation of cardiovascular disease, and certainly similarities in pathology exist. A recent study has used the antiplatelet drug aspirin (acetylsalicylic acid) in men with vasculogenic ED and a high mean platelet volume (associated with platelet activation); this study concluded that taking 100mg aspirin daily significantly reduced the symptoms of ED[68]. However, daily aspirin therapy is associated with enhanced bleeding risks, and this raises the question, would a dietary antplatelet be similarly successful? Fruitflow® has been shown to block expression of P-selectin on the platelet surface and to prevent GPIIbIIIa from binding; it has similar effects to low dose aspirin[9]. Thus we hypothesise that these characteristics, combined with its better safety profile, merit further investigation of Fruitflow® in ED.

5.2. Allergic responses

With its links to both inflammation and the immune system via the complement pathway, the allergic response is another area in which platelets are implicated. Platelet-leukocyte aggregates are well documented in allergic responses[69], and investigation of new pathways by which platelets can be suppressed without compromising their primary haemostatic function is an area of active research[70]. While there is very little available information on nutritional interventions which help to suppress allergic responses, dietary antplatelets may be an option worth exploring.

6. Conclusions

Platelets have multifaceted functions which give rise to 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 responding to – and in complicating – inflammatory and infectious illnesses grows, it becomes ever clearer that platelet-targeted treatments are necessary outside the field of CVD. Dietary antplatelets such as Fruitflow® could help to 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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References

Platelets: the missing link


Smith, J.E., 2017.


Hilberg, T., et al., 2014.

61.

669.

39.

406.

354

379


Whyand, T., et al., 2018.


