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Platelet hyperactivity in COVID-19: Can the tomato extract Fruitflow® be used as an antiplatelet regime?

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ABSTRACT

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus is now considered a global public health threat. The primary focus has been on reducing the viral spread and treating respiratory symptoms; as time goes on, the impact of COVID-19 on neurological and haemostatic systems becomes more evident. The clinical data suggest that platelet hyperactivity plays a role in the pathology of COVID-19 from its onset and that platelets may serve critical functions during COVID-19 progression. Hyperactivation of blood platelets and the coagulation system are emerging as important drivers of inflammation and may be linked to the severity of the 'cytokine storm' induced in severe cases of COVID-19, in which disseminated intravascular coagulation, and platelet hyperactivity are associated with poor prognosis and increased risk of mortality.

We propose that targeting platelet hyperactivity in the early stages of COVID-19 infection may reduce the immunothrombotic complications of COVID-19 and subdue the systemic inflammatory response. Lowering baseline platelet activity may be of particular importance for higher-risk groups. As an alternative to antiplatelet drugs, an inappropriate intervention in public health, we propose that the dietary antiplatelet agent Fruitflow®, derived from tomatoes, may be considered a suitable therapy. Fruitflow® contains antiplatelet and anti-inflammatory compounds that target the mechanisms of platelet activation specific to COVID-19 and can be considered a safe and natural antiplatelet regime.

Introduction

Coronavirus disease 2019 (COVID-19) has already has claimed total deaths of 1,300,062 worldwide as of 13 November 2020, and cases worldwide are increasing daily. During its acute stage, the hallmarks of COVID-19 include an elevated inflammatory response (cytokine storm), respiratory symptoms, multi-organ dysfunction syndrome, and significant thrombotic complications [1,2]. The SARS-CoV-2 virus also has neuro-invasive properties, which are linked to respiratory failure in the acute infection phase[3], and to a range of brain disorders which manifest in the chronic stage (myopathies, neuropathies, GBS, and brainstem encephalitis)[4]. The severity of both respiratory and neurological effects appears linked to the strength of the cytokine storm [5].

COVID-19 presents various effects on the haemostatic system, including increased production of inflammatory cytokines, dysregulated coagulation parameters, increased D-dimers, mild thrombocytopenia, increased microthrombi, and platelet hyperactivity associated with increased spontaneous platelet aggregation [6]. The associated coagulopathy, especially disseminated intravascular coagulation (DIC) and reduced platelet count, is associated with poor prognosis, increased risk of thrombosis, and increased risk of mortality [6–9]. While the patterns of thrombotic complications appear clear and universal in patients with severe COVID-19, the platelets' role and in particular the role of platelet hyperactivity in COVID-19-induced coagulopathy is only now being examined. Emerging data suggest that blood platelets may serve critical functions during COVID-19 progression. Therefore, the maintenance of normal haemostasis and blood flow is critically important in COVID-19. This may be particularly relevant to some groups known to be at increased risk of mortality from COVID-19 complications, such as black and Asian ethnic groups [10], people with underlying non-communicable diseases, such as diabetes or atherosclerotic manifestations [11,12], people living in areas of high air pollution[13] and, potentially, people more at risk of 'long COVID', e.g., women over the age of 50[14].

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COVID-19 and blood platelet function

Platelet influence on general viral infection–mediated thrombosis has already been demonstrated [15], but its impact on COVID-19 illness may be more significant than expected. Due to their relative abundance in the circulation at sites close to the initial target cells of the SARS-CoV-2 virus, blood platelets may well be the first blood cells to interact with SARS-CoV-2 in large numbers. It is likely that they may internalise SARS-CoV-2 and play a significant role in inducing the first wave of response.

Direct exposure of blood platelets to SARS-CoV-2

The initial stage of infection involves replication of the SARS-CoV-2 in epithelial cells of the respiratory tract. SARS-CoV-2 is an upper respiratory virus that, similarly to influenza, becomes problematic when it reaches the lower lung epithelial cells. The lung epithelial cells comprise the alveolar sacs' lining and are located close to the capillary endothelial cells. This proximity is critical for gas exchange: platelets are also present nearby and in large numbers, as they play an essential supporting role in the capillary, mediating endothelial integrity [16,17]. The continual interaction between capillary platelets and endothelium brings large numbers of platelets into contact with the reproducing SARS-CoV-2 virus, and some internalisation of the virus is likely, as previously seen for other coronaviruses. Human blood platelets from influenza-infected patients have previously been shown to contain influenza particles[18].

Immediate consequences of platelet / SARS-CoV-2 interaction

In human blood platelets, the initial response to single-stranded viral RNA is mediated predominantly by Toll-like receptor 7 (TLR7) [19]. Internalised influenza viral particles co-localize with TLR7 in the lysosomes [18]. Activation of TLR7 leads to platelet α-granule release in an AKT- and p38-dependent manner, followed by the interaction of platelets with neutrophils via P-selectin and CD40L [19]. In addition, platelet TLR7 leads to complement C3 release, which pushes neutrophils to release their DNA by formation of neutrophil extracellular traps in the process of NETosis [18]. C3-mediated NETosis does not require neutrophils' attachment to the vascular bed, and netting neutrophils can circulate in the blood as extracellular traps [18]. While these capture virus particles and protect from viral challenge [20], they are also highly prothrombotic. When dysregulated, such neutrophil activation may induce intravascular coagulation – thrombin, generated from coagulation, can activate C3 and, consequently, the wider platelet population and the entire pro-inflammatory complement cascade [21]. Endothelial damage, now established as a typical response to COVID-19 disease, also releases other platelet agonists and further exacerbates platelet hyperactivity [22]. Thus early-stage exposure of platelets to SARS-CoV-2 via the lung capillary endothelium can initialise a cascading reaction spreading to the whole haemostatic system, producing a hypercoagulable state even in the early stages of the disease.

Impact of later-stage COVID-19 illness on blood platelets

SARS-CoV-2 causes a change in spontaneous platelet aggregation, an important contributing factor in blood clot formation. The virus triggers genetic and functional changes in platelets [23]. Using platelet RNA sequencing, altered gene expression profiles have been observed in pathways associated with ubiquitination, antigen presentation, and mitochondrial dysfunction. The resting platelet activation levels in patients with COVID-19 have been shown to be higher than in healthy donors. COVID-19-affected platelets exhibited increased aggregation, enhanced binding to fibrinogen and collagen (upregulation of the MAPK pathway), and increased TxA2 generation. Platelet interactions with neutrophils, monocytes, and T cells were similarly raised in the COVID-19 group.

Hottz and colleagues [24,25] also demonstrated that COVID-19 is associated with platelet hyperactivity. The platelets of critically ill COVID-19 patients showed enhanced expression of P-selectin and CD63 and enhanced platelet aggregation compared with patients with mild COVID-19 infection. The hyperactive platelets from the severely ill group were shown to induce monocyte-derived tissue factor (TF). These findings were accompanied by elevated blood fibrinogen and D-dimer levels. The authors showed that pretreating platelets from donors with severe COVID-19 with antibodies that block platelet-dependent TF generation (anti-P-selectin antibody, or the anti-αIIb/β3 antibody abciximab) reduced the generation of TF by monocytes, thus linking the phenomenon directly to platelet hyperactivity [25]. Platelet hyperactivity was linked to a worse outcome, with an increased need for invasive mechanical ventilation and high mortality [25]. Thus newly emerging evidence directly links platelet hyperactivity with TF, thrombin-driven dysfunctional coagulation and immunothrombosis, as seen in patients with COVID-19.

Wider consequences of SARS-CoV-2-induced platelet activation

An abundance of evidence has long demonstrated the influence of platelets on physiological systems other than haemostasis. Platelets are key mediators in initiating and regulating inflammation. Inflammatory cytokines released in increasing amounts as COVID-19 progresses can directly affect platelet function and further contribute to their thrombotic tendency. IL-6, IL-1b, and TNF-α are all elevated in the plasma of patients with COVID-19 [25,26]. Both IL-6 and IL-1b can lead directly to platelet hyperactivation [27], and both of these cytokines can augment agonist-induced platelet aggregation [28,29]. TNF-α is particularly linked with age-related platelet hyperactivity [30]. Overall, these inflammatory cytokines can amplify platelets' thrombotic response and lead to further activation and platelet exhaustion, potentially leading to mild thrombocytopenia as is observed with COVID-19. The amplified thrombotic response also contributes to the severity of the cytokine storm generated, thus affecting the severity of respiratory and neurological symptoms experienced.

After the early stages of infection, with the onset of the adaptive immune response, platelet interaction with the immune system also comes into play. Platelet-FcγRIIa may recognize IgG antibodies from viral particles, resulting in platelet-derived thrombin generation [31]. Interactions with the immune system contribute to inflammation of the respiratory tract that may, in turn, result in more severe lung injury.

Implications of platelet hyperactivity for COVID-19 patients

The most serious acute consequences of platelet hyperactivity – widespread deposition of microthrombi in lungs and other organs, and DIC – have so far only been reported in severe cases of COVID-19. In such cases, anticoagulants such as LMW heparins and high doses of antiplatelets are a component of ICU treatment; proof of efficacy in reducing mortality and / or further complications is still under evaluation [32].

Clearly, such treatment is neither practical nor suitable for most COVID-19 patients who contract a mild / medium severity illness. However, targeting platelet hyperactivity may well help to prevent or delay the progression of the illness from mild to more serious if this could be achieved in the early stages of illness. The studies recently published by Manne et al. [23] and Hottz et al. [24] show that it is possible to block the production of TF (and by extension, thrombin) 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 [17,25,24]. A treatment such as this is likely to be most effective during the early stages of COVID-19 illness, before viral effects amplify to produce a cytokine storm.

Early stage focuses on the platelet to prevent the upregulation of inflammation and reduce TF and thrombin generation could be of particular benefit in population groups characterised by resting platelet hyperactivity. For example, inflammation may be exacerbated in patients with hypertension, cardiovascular disease, and obesity, all associated with baseline platelet hyperreactivity [33,34]. Diabetics also experience significant platelet hyperactivity, linked to increased circulating microparticles and hypercoagulability [35]. Several studies have shown that patients with these underlying comorbidities suffer more severe COVID-19 complications and have a worse outcome [11,12]. Living in areas with mild to severe air pollution is again linked to resting platelet hyperactivity and reported to significantly worsen the course of COVID-19 illness [36]. There may also be implications for the condition referred to as 'long COVID', where symptoms persist in the absence of acute infection for weeks or months. Persistent activation of the haemostatic system is likely in such cases, although there is as yet no available data on which to draw.

If reducing platelet function during the early stages of COVID-19 affects the progress of the disease, this could have a significant impact on the numbers of serious cases, the development of COVID-19-related thrombotic complications, and the severity of chronic neurological conditions post-COVID-19. However, while this is potentially a worthwhile intervention, using antiplatelet drugs to limit platelet function in individuals not at raised risk of a cardiovascular event is contraindicated on safety grounds, due to the increased risk of internal bleeding [37]. Thus a different approach to suppressing platelet function is needed.

Hypothesis and arguments for the use of the dietary antiplatelet Fruitflow®

Data currently available suggest that a directed blockade of platelet P-selectin and/or other key platelet-activation pathways may interfere with the platelet hyperreactivity observed in COVID-19 [17,25]. This may help prevent / slow the TF – thrombin-mediated thrombotic complications of COVID-19 and impact the severity of disease experienced. Because a modest rate of bleeding and thrombocytopenia have been reported in COVID-19 patients, the impact of such treatment on overall haemostasis must be carefully considered [38]. We suggest that a dietary antiplatelet may be suitable for use to achieve the desired platelet suppression, while antiplatelet drugs would be inappropriate in such a public health setting.

During the last two decades, numerous studies have demonstrated that water-soluble components found in tomatoes inhibit blood platelet aggregation both in vitro and in vivo [34,39–41]. This water-soluble tomato extract (trade name Fruitflow®) was the first food ingredient to be given an EC-authorised health claim under the 'emerging science' category, after evaluation by EFSA in 2009 (EFSA Journal 2010). The approved claim was 'Helps to maintain normal platelet aggregation, which contributes to healthy blood flow'. Fruitflow® is now an established naturally-derived functional food ingredient, marketed globally. Multiple human studies have shown that typically, consumption of Fruitflow® causes a platelet suppression of up to 25%, relative to baseline status [34].

Proteomic studies have shown that the tomato-derived compounds in Fruitflow® (nucleosides, derivatives of simple phenolics, and flavonoid glycosides) affect platelet proteins with platelet structure, platelet coagulation, platelet membrane trafficking, platelet secretion, redox system proteins, and HSP70s [42]. The downstream effects of these interactions with the platelet proteome are seen in the suppression of P-selectin expression by the platelet and reduction in integrin αIIb/β3 activation [42]– both indicated by recent research to be potential targets for the blockade in COVID-19. TF-mediated thrombin generation is also reduced [34] – again, a pathway specifically related to effects caused by SARS-CoV-2.

As described earlier, activation of the inflammatory pathways plays a critical role in the initiation and progression of endothelial dysfunction in COVID-19. The influence of Fruitflow® on the inflammatory response of macrophages and endothelial dysfunction in human umbilical vein endothelial cells (HUVEC) has recently been investigated [43]. Navarrete et al. [44] also showed the effects of aqueous tomato extract on pro-inflammatory cytokine expression in LPS-activated monocyte-derived THP-1 macrophages. Cytokines TNF-α and IL-1β were suppressed, along with activation of NF-κB. Fruitflow® may also protect the endothelium through its effects on intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). These two critical adhesion molecules are expressed on endothelial cells and mediate adhesion of leucocytes and their interactions with inflamed endothelial cells, leading to endothelial damage [45]. Schwager et al. (2016) showed that Fruitflow® significantly decreased the production and the gene expression of ICAM-1 and VCAM-1 in activated HUVEC [43]. This suggests that Fruitflow® may be capable of altering some of the pathologies typically seen in endothelial dysfunction, a typical response to SARS-CoV-2.

Fruitflow® is a dietary antiplatelet, with a reversible mode of action and a gentler antiplatelet effect than antiplatelet drugs such as aspirin, clopidogrel, prasugrel, etc. These characteristics render it suitable for use as a daily preventative antiplatelet regime where antiplatelet drugs are inappropriate [46,47]. The cumulative antiplatelet effect of aspirin, when taken daily, is well known and reflects its irreversible disabling of platelet COX-1 and associated signalling. Fruitflow®'s effects are not cumulative in this way, as its effects do not irreversibly disable platelet signalling pathways. As a result, Fruitflow® does not extend the bleeding times in the same way that antiplatelet drugs can. This is illustrated by an intervention study involving 47 healthy subjects, which showed that overall, daily aspirin supplementation may be viewed as approximately three times as productive as daily Fruitflow® supplementation, but is accompanied by an average increase in time to form a primary clot in flowing blood (PFA-100 closure time) of 135% [42]. In contrast, Fruitflow® supplementation increases the time to clot by only 40%, so that the parameter remains within its normal range. These more moderate effects, which can be related to the reversibility of the antiplatelet action of Fruitflow® rather than its mode of action per se, render it a possible option for use by the general population as a safe dietary antiplatelet.

To summarise, the consumption of antiplatelet tomato components as Fruitflow® reduces platelet hyperactivity and inflammation and may also help prevent endothelial dysfunction. An array of extensive basic, mechanistic, compositional, and human trials is testimony to its vascular benefits. Its modes of action are appropriate for use against platelet activation caused by SARS-CoV-2, targeting P-selectin and integrin αIIb/β3 activation, and the TF-thrombin-driven amplification of coagulation. We suggest that consuming Fruitflow®, especially before or during the early stages of COVID-19 illness, may have an effect on the severity of illness experienced. It may particularly benefit people who are more vulnerable to the development of endothelial / platelet dysfunction. It is a safe dietary antiplatelet and should be investigated as a potentially useful intervention for prevention of thrombotic disorders in COVID-19.

Declaration of Competing Interest

Dr. Niamh O'Kennedy is the chief scientific officer of Provexis PLC, and Professor Asim K. Duttaroy is a member of the Scientific Advisory Board of Provexis PLC.

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