

# **Micronutrients, non-nutrients and Mediterranean diet: a potential protective role against COVID-19 through modulation of PAF actions and metabolism**

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**Abstract:**

The new coronavirus disease 2019 (COVID-19) pandemic is an emerging situation with high rates of morbidity and mortality, in the pathophysiology of which inflammation and thrombosis are implicated. The disease is directly connected to the nutritional status of patients and a well-balanced diet is recommended by official sources. Recently, the role of platelet activating factor (PAF) was suggested in the pathogenesis of COVID-19. In the present review several micronutrients (vitamin A, vitamin C, vitamin E, vitamin D, selenium, omega-3 fatty acids, minerals), phytonutrients and Mediterranean diet compounds (olive oil, fish, honey, plant foods) with potential anti-COVID activity are presented. We further underline that the well-known anti-inflammatory and anti-thrombotic actions of the investigated nutrients and/ or holistic dietary schemes, such as the Mediterranean diet, are also mediated through PAF. In conclusion, although there is no single food to prevent coronavirus, the aim is to follow a healthy diet containing PAF inhibitors in order to target both inflammation and thrombosis and try to avoid or/and reduce the deleterious effects of the COVID-19 epidemic.

**Key words:** COVID-19, Platelet activating factor, thrombosis, inflammation, Mediterranean diet, PAF-inhibitors

**Abbreviations:**

PAF: Platelet Activating Factor; PAF-CPT: dithiothreitol-insensitive CDP-choline: 1-alkyl-2-acetyl-*sn*-glycerol cholinephosphotransferase; Lp-PLA<sub>2</sub>: lipoprotein associated phospholipase A<sub>2</sub>; ACE2:angiotensin converting enzyme 2; TLR: Toll-like receptor

## Introduction:

The new coronavirus disease 2019 (COVID-19) pandemic is an emerging situation with high rate of infectivity, morbidity and mortality [1]. The pathophysiology of the disease involves a cytokine storm and the activation of thrombotic pathways [2]. It was recently documented that the disease is directly connected to the nutritional status of severely and critically ill patients in Wuhan, China [3]. Although “there is no diet to prevent coronavirus” [4] and there are limited applied clinical nutrition protocols for COVID-19 patients [5–7], the focus of the international community shifts to recommending a healthy dietary pattern [8], intended to control inflammation and thrombosis, which accompany the syndromes’ complications [8]. Indeed, a well-balanced diet ensures the proper functioning of the immune system [4] and several micro-constituents alone or as part of a healthy dietary pattern, such as the Mediterranean diet, play a role in viral infections [9], inflammation [10] and thrombosis [11, 12]. A key molecule implicated in COVID-19 pathology is platelet activating factor (PAF), as recently highlighted by our group [2, 13]. More particularly, PAF is a glyceryl-ether phospholipid (1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) [14], which is a potent mediator of inflammation and thrombosis [15, 16]. It is produced by various cells such as platelets, endothelial cells, macrophages, monocytes, neutrophils and other cells continuously or upon inflammatory stimuli [15]. It is noted that the main biosynthetic enzymes of PAF are Lyso-PAF-acetyltransferases and dithiothreitol-insensitive CDP-choline: 1-alkyl-2-acetyl-*sn*-glycerol cholinephosphotransferase (PAF-CPT). PAF is catabolized by PAF acetylhydrolase or lipoprotein associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) [15]. PAF levels, PAF induced platelet aggregation and the activity of its metabolic enzymes correlate with various clinical states such as asthma, stroke, atherosclerosis, heart failure, cancer, kidney disease and viral diseases [9, 15, 17].

With respect to COVID-19, PAF is a highly pyrogenic agent [18] and it affects the activity of angiotensin converting enzyme 2 (ACE2) [19], which is used as a receptor facilitating the entrance of SARS-CoV-2 into the cells [20]. According to a lipidomic analysis human cells infected with the coronavirus HCoV-229E are enriched in PAF [21]. Moreover, oxidized phospholipids, which contain PAF and PAF-like lipids [22, 23] have been detected in the respiratory system of patients with SARS-CoV-1 and seem to increase cytokine production and lung injury via Toll-like receptor (TLR)4 [24]. Another similarity between COVID-19 and PAF is that they are both connected to Kawasaki-like disease in children [25]. PAF has been also found to increase phagocytic capacity in equine alveolar macrophages [26] and its levels are increased in acute pulmonary disease [27], pulmonary hypertension [28] and sepsis [29]. Interestingly, the first-line drugs used in the COVID-19 epidemic, such as chloroquine have been also found to reduce PAF induced pulmonary edema [30]. Hopefully, specific inhibitors can modulate the action of PAF, such as rupatadine [31] and have been proposed as potential candidate therapeutic compounds against COVID-19 [13]. Inversely, widely prescribed medicines, such as statins or antiretroviral drugs with pleiotropic actions also influence PAF [32, 33].

The inhibitors of PAF found in natural products and microconstituents of the diet are of increasing interest [11, 34]. In fact, diet can directly affect PAF induced platelet aggregation, PAF levels and/ or the activity and expression of PAF metabolic enzymes [35] or can act indirectly by modifying its environment (i.e. oxidative stress) [23]. Furthermore, the modulation of PAF by dietary parameters has been shown to affect the manifestation of disease [36]. Given the newly suggested role of PAF and its dietary inhibitors in the COVID-19 epidemic in limited works [2, 10, 13, 37], the scope of the present mini-review is to thoroughly present the potential anti-PAF actions of nutrients “protecting” against COVID-19. We further

suggest that the well-known anti-inflammatory and anti-thrombotic actions of micronutrients, non-nutrients and/ or holistic dietary schemes are also mediated through PAF.

### **Micronutrients COVID-19 and PAF**

Several micronutrients have been suggested to act as immunomodulatory agents against COVID-19 [38]. Their main actions along with their potential anti-thrombotic and anti-PAF effect will be briefly presented.

#### *Vitamin A*

Carotenoids have immunoregulatory actions including reducing free radicals [39] and pro-inflammatory molecules, such as IL-2 and TNF- $\alpha$ . Moreover, vitamin A downregulates IFN $\gamma$  production, an action which is more evident in a high oxidative stress environment [40]. Vitamin A is implicated in respiratory diseases since it plays a role in the formation of healthy mucus layer [41] and its overt or subclinical deficiency increases morbidity and mortality from infections and respiratory diseases [41].

Retinoic acid can modulate the gene expression of PAF-receptor [42] and acts synergistically with PAF to activate the inducible prostaglandin synthase gene [43]. Prostaglandins synthesis contributes to gastric mucosal defense, although different effects are attributed to the many kinds of prostaglandins [44]. It is also noted that serum retinol has been inversely related to the activity of Lp-PLA<sub>2</sub> in epidemiological studies [45]. The interplay of vitamin A and PAF in immunity is also highlighted by the fact that the host-versus- graft reaction, in which PAF is implicated [46], is enhanced by high levels of vitamin A (34).

#### *Vitamin C*

Vitamin C acts as an antioxidant and interferes with the immune system [47]. It is involved in the function and integrity of mucosal cells, the normal functioning of T cells while it also

exerts antimicrobial effects [37]. Vitamin C concentration is high in leukocytes and it is utilized in case of infection [48]. Vitamin C reduces the risk, the severity, and the duration of different infectious diseases, its status has been associated with pneumonia [49] and the supplementation with vitamin C may prevent and treat respiratory and systemic infections [47]. Therapeutic doses of vitamin C (24 gr/day intravenously, for seven days) are currently being tested in hospitalized COVID-19 patients [7]. However, official sources pinpoint that there is no evidence yet to support intravenous super doses of vitamin C in the management of COVID-19 [50].

In addition, vitamin C affects thrombosis and fibrinolysis in high risk patients with cardiovascular disease and diabetes [51], an action already suggested in the 70's [52]. In the same context, it has been found to reduce PAF levels in vitro [53]. Indeed, vitamin C reduces oxidative stress [47], which is a strong trigger for synthesis of PAF [54] and its receptor [55]. It is also noted that in frailty, which worsens COVID-19 outcomes [56] the PAF catabolic enzyme Lp-PLA<sub>2</sub> is increased (suggesting its upregulation to counter-balance PAF levels) while anti-oxidant status is decreased (vitamin C, E,  $\alpha$ -tocopherol, biological anti-oxidant potential, total thiol levels) [57]. Vitamin C status could thus affect the inflammatory and micro-thrombotic environment including PAF and the morbidity of COVID-19 *per se*.

### *Vitamin D*

Vitamin D exerts antimicrobial and anti-oxidant effects and supports the immune system against respiratory infection [58]. According to a meta-analysis vitamin D supplementation reduces the risk of acute respiratory infections [59], has been inversely related to hepatitis viral load [60] and improves antibacterial immunity in HIV-1 patients [61]. An inverse association between mean levels of vitamin D and the number of COVID-19 cases/1 M was recently reported in a cross-sectional European study whereas a UK study did not find an association

between the vitamin's status and COVID-19 risk [62]. Moreover, low levels of vitamin D were found in COVID-19 positive patients [63] or hospitalized patients with COVID-19 [64] and have been connected to the severity of the disease [65–67]. The hypothesis that vitamin D may explain susceptibility to COVID-19 infection in dark colored skin individuals do not seem to be valid [62]. It is noteworthy that several clinical trials are on the way regarding the role of vitamin D in prevention and treatment of COVID-19, reviewed elsewhere [48].

*In vitro* data suggest that 1,25-dihydroxyvitamin D<sub>3</sub> reduces the secretion of the catabolic enzyme PAF-AH from placenta macrophages [68], which implies an interrelation of PAF with the vitamin. Moreover, paracalcitol has an anti-inflammatory and anti-PAF action in hemodialysis patients inhibiting PAF/thrombin-induced platelet aggregation, reducing the activity of PAF biosynthetic enzymes and increasing the activity of the catabolic enzyme of PAF, i.e. PAF-AH [69]. Last but not least, the connection of vitamin D with PAF is further substantiated by the known anti-thrombotic effects of vitamin D [70].

### *Vitamin E*

Vitamin E acts as an antioxidant and has a role in the proper function of immune system [58]. Indeed, it protects cell membranes, including those of immune cells from lipid peroxidation [71]. In cases of influenza infection the lung levels of vitamin E are reduced [72], while supplementation with the vitamin reduces the severity and duration of the disease [73, 74]. In the same context, in a meta-analysis of randomized controlled trials vitamin E reduced CRP levels [75]. A combination of vitamin E and C has been recently proposed for ameliorating cardiac injuries of critically ill COVID-19 patients, which further underline their role in the COVID-19 disease [76].

Vitamin E deficiency is connected to increased PAF synthesis in rat polynuclear cells [77]. Moreover, vitamin E inhibits PAF induced platelet aggregation [78–80] and PAF synthesis

[81]. In addition, lycopene alone or in combination with  $\alpha$ -tocopherol reduces PAF synthesis in stimulated endothelial cells [82], which can further blunt the inflammatory cascade. Vitamin E and increased Lp-PLA<sub>2</sub> have been associated with decreased asthma development [83], while the vitamin may indirectly affect Lp-PLA<sub>2</sub> since it improves LDL quality, in which the enzyme is attached [84]. However, high levels of vitamin E ingested as a supplement (1500 IU for two weeks) seem not to influence the concentration of lyso-PAF [85]. In total, vitamin E can affect PAF levels, metabolism and its actions on platelets, i.e. the pro-thrombotic state.

### *Selenium*

Selenium has been proposed to potentially play a role in COVID-19 prevention, since in the form of sodium selenite it can oxidize thiol groups in the virus protein disulfide isomerase and thus inhibit the entrance viruses into the cell [86]. It also has an antioxidant role since it is a structural component of glutathione peroxidases, a family of antioxidant enzymes [87]. In parallel, selenoprotein H is involved in redox transcription while selenoprotein K found in the endoplasmic reticulum, is involved in calcium flux in immune cells which is a critical step in immune response [87]. Selenium deficiency is associated with an increase in inflammatory molecules [88], while selenium supplementation has been found to improve the response against H1N1 virus [89]. In mouse models of asthma there seems to be a reverse-U relation with selenium concentration since too little or too much contributed to asthma attenuation [90]. The relation of selenium with the immune system is further corroborated in hospitalized patients with COVID-19, in which selenium levels were found sub-optimal [64]. Moreover, good selenium status, as assessed by the selenium hair content, has been connected to a higher recovery rate from COVID-19 [91].

The relation of selenium and PAF can be considered under the prism of the effects of selenium on oxidative stress and phospholipid metabolism. Firstly, the modulation of oxidative



stress by selenium could affect PAF metabolism, as for example it deactivates Lp-PLA<sub>2</sub> [23] and increases PAF synthesis [54]. Secondly, selenoprotein I is implicated in phospholipid biosynthesis [87]. Moreover, PAF production is increased in case of selenium deficiency in endothelial cells [92, 93] possibly through activation of its biosynthetic enzyme lyso-PAF-acetyltransferase [92]. It is noted that the content of diet in selenium did not alter Lp-PLA<sub>2</sub> in rats [94]. Last but not least, selenium deficiency is associated with arterial thrombosis and selenium seems to decrease platelet aggregation [95]. It can be thus hypothesized that worse outcomes of COVID-19 on the grounds of selenium deficiency may be at least in part attributed to increased PAF and an associated pro-thrombotic state.

### *Omega-3 fatty acids*

Omega-3 fatty acids have anti-inflammatory and anti-thrombotic effects [10], while they may interfere with virus entry and replication through modulation of lipid rafts [96]. The results from animal studies show that mice with *Klebsiella pneumoniae* or *Streptococcus pneumoniae* had an upregulated immune defense and less bacterial burden when fed omega-3 fatty acids [97, 98]. However, it is noted that fish oil-fed mice display impaired resistance to influenza infection [99, 100] denoting a more complex immunomodulating effect of omega-3 fatty acids.

Omega-3 fatty acids also exert antithrombotic effects by various mechanisms including a reduction in thromboxane synthesis [101] and PAF [102, 103]. Omega-3 fatty acids incorporate in cell membrane and may regulate the activity of PLA<sub>2</sub> and thus Lyso-PAF production, which is a prodrome molecule for PAF production [104]. DHA inhibits PAF increase in cell lines [105]. Moreover, omega-3 can reduce PAF production in HUVEC endothelial cells [103]. In cases of endotoxemia, which is also observed in seriously ill COVID-19 patients [106], linolenic acid has been found to reduce PAF production in Sprague-Dawley rats [107]. In addition, a diet rich in fish oils (10%) has been found to reduce PAF and LTB<sub>4</sub> [108]. As far as PAF enzymes are

concerned, a negative association has been documented with the PAF catabolic enzyme Lp-PLA<sub>2</sub> and adipose tissue omega-3 fatty acids [109] while the effects of supplementation did not change the enzyme's activity in healthy adults [110] but decreased the enzyme in volunteers with stable angina [111] and hypertriglyceridemia [112]. It is noted that Lp-PLA<sub>2</sub>, increases as a result of increased PAF in order to catabolize it, so the trend for an inverse association of Lp-PLA<sub>2</sub> with omega-3 fatty acids, implies a negative association with PAF. Moreover, results from a cross-sectional study of our group have shown that omega-6 fatty acids were positively correlated with PAF-CPT while no significant correlations were observed with omega-3 fatty acids and PAF or its enzymes [113].

#### *Zinc, copper, magnesium and iron*

Zinc plays a role in maintaining the integrity of mucosal cells and antigen response [37]. It has antimicrobial, anti-inflammatory and antioxidant effects [37]. Moreover, it has been found to inhibit the activity and replication of coronavirus (SARS-CoV-1) [114] while it has a role in interferon- $\gamma$  production [115]. Zinc deficiency can increase susceptibility to various infections, including those of the respiratory system [116]. Zinc supplementation in mechanically ventilated trauma patients was related to decreased risk of ventilator-associated pneumonia [117]. Moreover, zinc may mediate the beneficial effects of the chloroquine, a drug which is widely used against COVID-19. Indeed, chloroquine is a zinc ionophore, which increases intracellular Zn<sup>2+</sup> levels [118].

Copper can prevent oxidative DNA damage and decrease inflammatory markers [37], since it is a part of antioxidant enzymes such as Zn-Cu-superoxide dismutase and ceruloplasmin [119]. Its deficiency is connected with an increase rate of infections [120], which may be related to its role in T-cell proliferation and NK activity [115]. On the other hand, macrophages can attack pathogens with high copper and as a result the concentration of copper

may be found increased in lung infection [121]. However, no direct connection to COVID-19 exists so far.

Iron participates in the differentiation and growth of epithelial tissue and the production of reactive oxygen species, which combat pathogens [58]. Supplementary iron intake has been found to reduce respiratory infections [122] while pulmonary iron modulation represents a defensive mechanism against various respiratory pathogens [123]. Despite the important role of iron in the immune system, iron-containing enzymes are essential for the replication of coronavirus [124] and the chelation of iron compounds may prove beneficial [37]. Iron can also modulate interferon production [115].

The interrelation of PAF with zinc, copper and magnesium is not very clear. A low zinc diet reduces platelet aggregation suggesting a role of this nutrient in haemostasis [125], while zinc and copper chelate complexes have a PAF inhibitory activity mainly attributed to stereochemical interactions [126, 127]. Chelating agents such as  $Mg^{2+}$ , reduce the activity of PAF biosynthetic enzymes, such as Lyso-PAF-acetyltransferase [128]. The relation of copper and iron with PAF has been investigated under the prism of copper and iron induced oxidation of lipids and PAF-related enzymes [23]. It is noted that metal- induced oxidative stress in the presence of superoxide can inactivate PAF acetylhydrolase [129] and thus potentially increase PAF levels. In addition macrophage responsiveness to PAF is altered by interferon [130] and protects against PAF induced injury [131], which may reflect an indirect connection of some minerals with PAF through interferon.

### *Phytochemicals*

Phytochemicals, such as polyphenols, act as antioxidants, modulate LDL oxidation [132], while they also exert anti-inflammatory, antiplatelet [133] and antiviral activity [134]. Resveratrol, is an inhibitor of SARS-CoviD-1 [135] and curcumin was recently reported to bind to the target receptors of SARS-CoV-2 [136]. In addition, curcumin combined with

vitamin C glycyrrhizic acid promotes interferons production and has immunomodulatory properties [137]. Luteolin binds to the surface spike protein of SARS-Cov-2 inhibiting in this way its entry into cells and it is a potential inhibitor of SARS-CoV-2 main protease (SARS-CoV 3CL) [138]. Moreover, lignans exhibit antiviral activity [139].

With respect to PAF, resveratrol and tyrosol as well as their acetylated derivatives inhibit PAF induced platelet aggregation [140] while curcumin is a PAF inhibitor [141] and plays a role in thrombosis and coagulation [142, 143]. Moreover, curcumin and phenolic compounds acting as antioxidants can modulate LDL oxidation [132] and the subsequent production of PAF and PAF-like lipids [22]. Their effect could be also directly exerted on PAF biosynthetic enzymes as evidenced by *in vitro* studies. Indeed, resveratrol and quercetin can inhibit both PAF main biosynthetic enzymes *in vitro* [144, 145], phenolic compounds reduce the activity of PAF biosynthetic enzymes in cell cultures stimulated with IL-1 $\beta$  [146] and flavonoids, have been documented to reduce Lyso-PAF acetyltransferase activity [147]. More particularly, pro-anthocyanidins [148], luteolin [147], quercetin [82, 149], hesperidin [149] and naringin [149] reduce the activity of Lyso-PAF acetyltransferase in cell lines. Licoricidin and other components were also documented to inhibit Lyso-PAF acetyltransferase [150]. Moreover, the antioxidant capacity of the diet, which is at least in part affected by phytonutrient intake, was inversely related with PAF levels and the activity of Lyso-PAF-acetyltransferase in healthy volunteers as evidenced by our group [34]. In parallel, PAF has been inversely related to antioxidant-rich foods (herbal drinks and coffee) [34]. Lignans, which have been proposed as an anti-COVID compound [139] are also PAF inhibitors [151]. Thus, the effects of flavonoids and other phytonutrients on PAF levels, actions as well as its metabolic enzymes generate the hypothesis that their anti-inflammatory and anti-thrombotic actions are at least in part mediated by PAF circuit.

Interestingly, certain natural flavonoids also have anti-PAF activity, in addition to their having anti-inflammatory actions and ability to block Conora virus binding to target cells [2, 13, 138].

### **Mediterranean diet, Mediterranean foods, COVID-19 and PAF**

Mediterranean diet including olive oil, fish, honey, fruits, vegetables and herbs is rich in polyphenols and other micro-constituents [35] and it has been inversely related to respiratory diseases [152], inflammation [153] and thrombosis [11, 35]. It is possible that the combination of phytochemicals as those occurring in the Mediterranean diet have amplified actions in comparison to sole compounds [154]. In fact, complex natural products mixtures synergistically target multiple networks involved in inflammatory and thrombosis [154]. The adoption of Mediterranean diet as a whole reduces PAF induced platelet aggregation in patients with 2 diabetes [155, 156]. Moreover, it has been suggested to be a potentially protective diet against COVID-19 [10, 157]. It is noted that the adoption of the Mediterranean Diet decreases length of stay and mortality in hospitalized patients >65 y of age [158, 159], which is of interest in the era of COVID-19 and the challenges of health systems.

Several natural products which are intrinsic characteristics of the Mediterranean diet such as garlic, salvia and olive oil have been proposed as additional measures for the prevention and treatment of COVID-19 [160]. These and additional Mediterranean foods will be briefly presented and a special reference will be provided on their relation with PAF and its enzymes

#### *Olive oil*

Olive oil contains monounsaturated fatty acids and several microconstituents with antioxidant and anti-thrombotic action, such as polyphenols [161] and polar lipids [36]. Its anti-oxidant, anti-inflammatory and anti-thrombotic action render it a candidate food against COVID-19

[160]. It is noted that olive oil polar lipids act as PAF antagonists [36, 162], while bioactive compounds have been also found in olive oil pomace and its byproducts [163]. From *in vitro* data it has been shown that olive oil polar lipids inhibit PAF-CPT which is a biosynthetic enzyme for PAF [144]. Moreover, Lyso-PAF-AT has been negatively associated with a dietary pattern rich in olive oil and whole-wheat products as documented by our research team [34]. Lastly, the consumption of a yogurt enriched with PAF-inhibitors isolated from olive-oil byproducts, led to attenuation of subclinical inflammation and platelet sensitivity to thrombotic stimuli in apparently healthy volunteers [164].

### *Fish*

Fish have anti-inflammatory and anti-thrombotic properties, while they exert beneficial effects in the respiratory tract (see also omega-3 fatty acids) [161]. Indeed, fish has anti-aggregatory effects mediated by PAF inhibition [155, 165, 166] attributed to polar lipids, neutral lipids [167] and other lipids, such as gangliosides [168]. Moreover, from *in vitro* data it has been shown that fish polar lipids inhibit PAF-CPT [144]. Fish polar lipids retard atherosclerosis in rabbits by down-regulating PAF biosynthesis and up-regulating PAF catabolism [169]. Interestingly, antibacterial properties of fish go hand in hand with their anti-PAF activity, suggesting that PAF antagonists and agonists in fish may also have antibacterial activity [170]. Last but not least, PAF has been inversely related to a healthy dietary pattern including legumes, vegetables, poultry and fish [34].

### *Honey*

Stingless bee honey has been found to inhibit TNF- $\alpha$ , IL-6 and interferon secretion from stimulated macrophages [171] and to reduce inflammation in animal models [172]. Honey has anti-bacterial properties thanks to its content of phenolic compounds, the production of

hydrogen peroxide and other mechanisms such as osmosis [173]. Moreover, it has been suggested to have a role against COVID-19 epidemic [174, 175], it has six compounds with affinity with the receptor active site of COVID-19 main protease according to a *in silico* approach [176] and is currently being tested in a clinical trial (clinical trial NCT04323345) [176]. It is noted that honey displays anti-thrombotic activity [177] and it especially acts as a PAF inhibitor [178]. In total, the anti-bacterial as well as the anti-thrombotic and anti-PAF effects of honey render it a potentially useful food against the COVID epidemic.

#### *Milk and yogurt*

Dairy products constitute a principal source of vitamin D, which has been proposed to play a role in the COVID-19 epidemic [65–67]. It is noted that milk, yogurt and fermented milk products also contain PAF inhibitors [179–181] with a trend for a more protective effect of goat yogurt [182].

#### *Plant foods*

Plant foods with antiviral properties have been recently reviewed as anti-COVID agents, since they prevent viral replication, enhance antibodies production against influenza virus, and improve T-cell function [161]. A recent work reported inhibition of COVID-19 with the use of molecular docking by plant terpenoids, such as Ginkgolide A [183], which is also one of the most potent PAF inhibitors [184]. Garlic and onion which are also used in many recipes of the Mediterranean diet also contain PAF inhibitors [185, 186]. Moreover, wild greens, which are rich in polyphenols have a postprandial anti-PAF effect [187].

#### *Wine and its products*

Although wine is not recommended by national bodies as a mean to fight coronavirus [8], the Mediterranean way of living and eating incorporates moderate wine consumption in its

philosophy. A Mediterranean background diet with moderate wine quantities could affect the pro-thrombotic status [188] and possibly the body's response to a virus. As it has been documented by our group wine consumption reduces PAF-induced platelet aggregation [189] and specific wine varieties affect PAF biosynthetic enzymes [190] in the postprandial state. Moreover, several bioactive lipids have been isolated from wines that exhibit anti-PAF biological activity [191–194] and reduce the activity of its biosynthetic enzymes in monocytes [145]. Last but not least, bioactive compounds with anti-aggregatory have been also isolated from grape pomace extracts [195], which may render winery by-products useful for the production of functional foods.

### **Conclusion**

In conclusion, although there is no single food to prevent and/or heal - treat coronavirus, the aim is to follow a healthy diet containing, among other beneficial ingredients, PAF inhibitors in order to target inflammation and thrombosis and try to avoid and/or reduce the deleterious effects of the COVID-19 epidemic.



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