

## Antioxidants associated with NSAIDs might even exacerbate the progress of SARS-CoV2 disease

To the Editor

A few years ago, a paper by Poljsak et al., reported quite unusual evidence that natural anti-oxidants, that is, vitamins, minerals, and phytochemicals, may have noxious rather than beneficial actions if abused.<sup>1</sup> According to these authors, the exceeding use of dietary supplements should lead to an "antioxidative stress," terminology used for the first time by Dundar and Aslan, to indicate the adverse effect of nature-derived anti-oxidants on the reactive oxygen species (ROS)-signaling system and the oxidative stress response, then leading to health disorders and immune or metabolic injury.<sup>2,3</sup> Obviously, both antioxidative and oxidative stresses are caused by an imbalance in the ROS signaling, which should lead to damages for the organism and might result in several pathological disorders.<sup>1</sup>

The widespread use of herbal and nature-derived compounds associated with nonsteroidal anti-inflammatory drugs (NSAIDs), to relieve early or mild symptoms in coronavirus disease 2019 (COVID-19) positive patients, might exacerbate the progress of the disease, even leading to chronic impairments and post-acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) sequelae (PASC), which a redox imbalance has been suggested to be associated with.<sup>4</sup> Actually, the action of the excess antioxidant compounds on the endothelial redox mechanisms, while SARS-CoV2 is acting, may cause redox imbalance. Flavonoids, actually, target endothelia, by modifying their physiology.<sup>5</sup>

So far, there is no clinical evidence about the ability of anti-oxidants to progress COVID-19 towards PASC; notwithstanding, the abuse of these substances, commonly considered completely harmless, may affect the potential of NSAIDs to rescue a complete health status.

This consideration comes from deeply observing the mechanisms underlying the activity of supplement anti-oxidants associated with anti-inflammatory drugs in the early treatment of COVID-19. Furthermore, previous evidence has reported that antioxidant supplements may act as ROS enhancers, if regularly assumed with pharmaceuticals and therefore exceeding the usual recommended dosage from raw food<sup>6,7</sup> and moreover ROS increase promotes venous thrombotic events.<sup>7</sup> Anyway, even the purported reduction of oxidative stress in endothelia and platelets, attributed primarily to the action of an enforced antioxidant supplementation, may promote thrombosis.

The first major consideration is that ROS are crucial signaling molecules for the platelet-mediated modulation of thrombotic events.<sup>8</sup> Cell redox homeostasis has a leading role in preventing

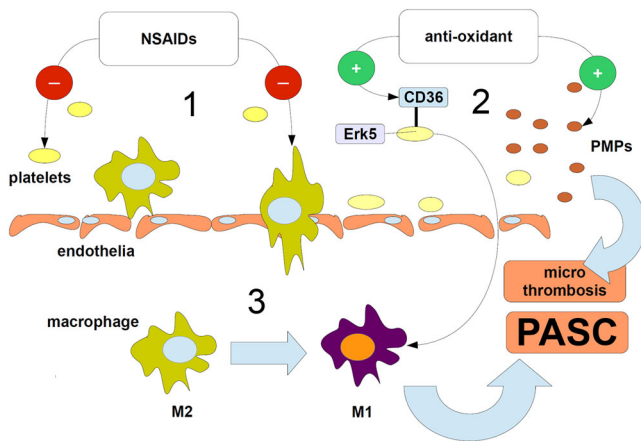
damage to the organism.<sup>9</sup> Adjusting the correct level of intracellular ROS, for example, is particularly important for the signaling of the mitogen-activated protein (MAP) kinase pathways in platelets.<sup>10</sup> MAP kinases are a family of at least four major components, namely the extracellular signal-related kinases 1 and 2 (Erk ½), the p38 kinase (p38MAPK), the c-jun N-terminal kinase (JKN1), and the big MAP kinase 1 or Erk5 (BMK1/Erk5). This latter is particularly crucial for the platelet function. The kinase Erk5 is expressed by platelets, its expression is finely regulated by ROS, and moreover, Erk5 acts as a keen sensor of the ROS level in platelets.<sup>10</sup> Upon ROS depletion, due to a strong antioxidant event, the role of Erk5 is impaired and platelet cannot tune their function on ROS signaling, so oxidized-low density lipoproteins activate platelet pro-thrombotic and pro-coagulant mechanisms via the CD36 receptor without the modulating activity of Erk5.<sup>10,11</sup> A marked reduction in ROS, activates mitochondria oxidative phosphorylation (OXPHOS), particularly in platelet mitochondria, which play an utmost role in platelet function.<sup>12</sup> When platelet mitochondria are particularly stressed, due to an increase in ATP production, ROS and calcium efflux, apoptotic mechanisms may occur,<sup>11</sup> so producing platelet microparticles (PMPs), which are particularly active in thrombotic mechanisms and can promote macrophage switching towards a pro-inflammatory M1 phenotype.<sup>13</sup> The apoptotic signal is particularly concerning if the cellular milieu is highly stressed, as occurring in platelet deficient of ROS signaling.

Delayed (not early) pro-thrombotic mechanisms and the prolonged activation of a pro-inflammatory status, might lengthen the SARS-CoV2 symptoms, and, at least theoretically, may reach possible PASC with fatigue.<sup>14</sup> How this might occur?

NSAIDs are able to reduce SARS-CoV2-related inflammation but the concurrent prolonged use of diet supplements should trigger antioxidative stress, particularly during the associated therapy formulation.<sup>15</sup>

Figure 1 briefly summarizes this overview.

Yet, NSAIDs do not act directly on the ROS production so disturbing the role of ROS as fundamental switchers of the Erk5/CD36-mediated regulation of platelet activation but help innate immune cells in scavenging the excess of pro-oxidant factors, particularly oxidized-lipoproteins, which trigger ROS increase. Anti-oxidants may cause a rapid depletion of ROS in strategic components of the endothelial function such as platelets, therefore inducing platelets apoptosis and formation of active PMPs, ultimately due to an enhanced mitochondria OXPHOS. A COVID-19 patient, treated with nature-derived anti-oxidants, such as hesperidin, quercetin, diosmin,



**FIGURE 1** Picture showing the paradoxical action of an antioxidant/NSAID combined therapy. (1) while an NSAID has both an antiaggregant and anti-inflammatory action, (2) the antioxidant supplement can induce a dysregulated CD36 function, and depletion of ROS, with an impairment in platelets mitochondria function, apoptosis and hence PMPs release, (3) which can switch monocytes and macrophages to the M1 pro-inflammatory phenotype. This may lead to a delayed micro-thrombosis and possibly to symptoms collectively gathered in the term PASC (or post-COVID). NSAID, nonsteroidal anti-inflammatory drug; PASC, post-acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) sequelae; PMPs, platelet micro-particles; ROS, reactive oxygen species

and so on, alongside with high dosage of NSAIDs, such as indomethacin, ibuprofen, ASA, or others, may feel better in a few days upon therapy. However, the empirical protocol regarding antioxidants dosage, in the absence of plasma ROS monitoring and sound clinical evidence, may lead to exacerbation in mitochondria redox activity, with induction of cell apoptosis and M1 pro-inflammatory macrophage switching. Reduction in platelets number is associated with a rapid increase in PMPs, so generating warnings about the possibility to develop micro-thrombotic events associated with a chronic subclinical inflammatory status, a circumstance that may mimic PASC.

The best recommendation would be to use NSAIDs, excluding paracetamol,<sup>16</sup> at the earliest upon the onset of COVID-19 symptoms and without using dietary supplements as therapy-associates, as nutraceuticals do not act as pharmaceuticals and may greatly impair the fine balance of ROS signaling pathways, leading to outcome practically opposite to the expected benefit from the antioxidant used.

Nutraceuticals should not be used with the same criteria and formulation of NSAIDs, they can be necessary during important micro-nutrient deficiency and always as nutrient supplementation, preferably via food intake.<sup>17</sup> People may be deceived about their use, trusting the consideration that natural products are completely safe

to treat COVID-19. Early COVID-19 symptoms must be treated preferentially and quite exclusively with NSAIDs.

#### CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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