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Letter to the Editor

Caffeic acid phenetyl ester and its ability to prevent viral infection - Some comments

A recent paper by Erdemli *et al*. on this journal reviewed the antiviral properties of caffeic acid phenetyl ester (CAPE) [1]. Recent literature showed that CAPE has also anti-inflammatory and immune-modulatory effects, as like as many other plant-derived phenolics [2] but its ability to exert an anti-inflammatory role has never been assessed in clinical trials, therefore, its activity on humans appears only presumptive. Yet, biomedical literature about CAPE effect on chronic inflammation and cancer appears quite promising and should encourage randomized controlled trials in patients. Its ability to affect *in-vitro* tumors is not so far than many other plant-derived phenolics, considered as anti-NF-κB agents [3], yet its antiviral potential might be attributed to independent pathways from interferon (IFN) induced by virus entry [4]. If CAPE is described only as an inhibitor of NF-κB activation, then some controversial issues would be raised. It is well-known that cells activate host-pathogen interactions, through the recognition of pathogen-associated molecular patterns by host sensors, which were defined as pattern recognition receptors. They include toll-like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), and DNA receptors. Then, virus may trigger these innate immune receptors. In the cell response, the activation of the nuclear factor-κB (NF-κB) transcription pathway is crucial for the immediate early step of immune activation. However, there are a variety of viral effectors that have been shown to prevent NF-κB signalling, namely, they should act as polyphenols at least three different levels: (a) TLRs, IκB kinase complexes and at the transcriptional level [5]. The antiviral activity of CAPE might be more complex than expected, therefore, as it might interfere with innate immunity as like as viruses, if it should act only on NF-κB, even by preventing its activation [5]. Which are the major targets of CAPE within an infected or inflamed cell? The paper by Erdemli *et al*. report some interesting suggestions [1]. Further consideration should be made.

As many other phenol-bearing molecules from plant biochemistry, CAPE should exert a protective role for plants and a proto-toxic activity in animals. CAPE has been described in the past to possess a prooxidant activity [6], particularly in the range 1.0-0.5 μM, interestingly the same range reported for its antiviral potential [4]. This apparently contradictory evidence, where CAPE is both a pro-oxidant and an antiviral molecule, deserves further considerastion about the many targets of CAPE activity and its pleiotropism within a defined cell. The paper by Erdemli *et al*. did not fully address this concern but expanding the debate may be of major interest to shed a light on the role of CAPE in propolis. The relationship with the redox machinery should involve also mitochondria, which activate mitochondria antiviral signaling (MAVS) regulome during their mitochondrial dynamics [7]. Mild induction of oxidative redox species, triggered by xenobiotics such as plant phenolics, may impair MAVS regulome and then activate a stress response from infected cells: This speculative hypothesis would suggest that CAPE may act, even indirectly, on signaling molecules upstream of IFN regulatory factor 3 (IRF-3), which are modulated by redox-dependent processes, and include MAVS and the tumor necrosis factor receptor-associated factors adaptors, all of which are sensitive to redox regulation [8]. CAPE is yet able to suppress IRF-3 activation, following inflammation or innate immune response [9] but this activity may follow cell regulation of virus infection, which allows that the E3 ubiquitin ligase RBCC protein interacting with PKC1 (RBCK1) binds to IRF-3 and targets it for ubiquitination and subsequent degradation through a proteasome-dependent pathway, to dampen the overexpression of RBCK1 by virus and reduce side effects as autoimmune disorders due to the excessive activity of IFNs [10]. It is presumable that a fine regulation of ROS-response at the mitochondrial turnover and MAVS regulome, induced by sub-micromolar doses of CAPE, may induce initially an IRF-3 mediated signaling by a mild-oxidative stress, inducing intracellular IFN, which then rapidly disappears while CAPE still acting on the redox system to activate antioxidant scavenging systems. Incubation times settled in *in-vitro* experimental research may hamper the ability to gain insights about the first minutes of activity of the natural compound, of which we can retrieve evidence mainly regarding its anti-oxidant potential and its anti-NF-κB action, while it is possible that the early action exerted by these phenolics targets fine equilibria involving mitochondria dynamics and their relationship with oxidative stress, even stimulating early IFN action.

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