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Letter to the Editor

In vitro and *in vivo* neuroprotective effect of caffeic acid phenethyl ester

Dear Editor,

Propolis is a mixture produced by honeybee, which have hundreds of polyphenols. Caffeic acid phenethyl ester (CAPE) [Figure 1], an active component of honeybee propolis has been determined to have antioxidant, anti-inflammatory, antiviral, and anticancer activities [1,2]. It has been used to prevent oxidative stress-based deterioration in cells/tissues/organs in both cell culture and experimental animals. Although, CAPE was shown to protect animals and cells against ischemia reperfusion injuries or anoxia, its effects on neurotoxins and neurotoxic pharmacological agents were not investigated extensively. It has been evaluated the potential of CAPE to induce neuritogenesis in pheochromocytoma (PC12) in terms of the involvement of this mechanism in the protection against the cell death induced by the dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP) (+), as well as the effects on the expression of proteins associated with axonal growth and synaptogenesis [3]. It has been shown in the study that CAPE protects PC12 cells from the cellular death induced by the MPP (+) by increasing the network of neurites, also, CAPE induced the formation, elongation, and ramification of neurites induced by the dopaminergic neurotoxin.

We have provided additional evidences and data for the mechanisms of protective effect of CAPE on neurotoxicity induced by various factors. We have shown that CAPE has a considerable neuroprotective effect on pentylenetetrazol (PTZ)-induced seizures in mice [4]. Oxidative stress and resultant dysfunction in PTZ-induced seizure could contribute to increased generation of reactive oxygen species and support the hypothesis that CAPE may improve the epileptic seizures by its antioxidant effects. When we look at the molecular mechanism of protective effect of CAPE, we noticed that CAPE effectively depressed endogenous overproduction of nitric oxide (NO), which is induced by ischemia reperfusion injury of rabbit spinal cord [5]. NO has been produced by the action of nitric oxide synthase enzyme (NOS). Ischemia causes a surge in NOS1 activity in neurons, increases NOS3 activity in vascular endothelium and later an increase in NOS2 activity in a range of cells including infiltrating neutrophils and macrophages. The primary product of the interaction between NO and superoxide radical (O_2^-) is peroxynitrite ($^-$ONOO), which is capable of either oxidizing or nitrating various biological substrates, especially in neurons. There is abundant evidence in the literature that the cellular death, particularly neuronal, provoked by NO may be apoptotic [6]. At this point, CAPE was found to exhibit profound inhibition of NFκB, a critical molecule in the apoptosis pathway [7]. In another study [8], we applied CAPE to prevent the outcomes or the total clinical symptoms of experimental autoimmune encephalomyelitis (EAE). CAPE exerted its anti-inflammatory effect by inhibiting ROS production at the transcriptional level through the suppression of NFκB activation, and by directly inhibiting the catalytic activity of iNOS. Totally, it inhibited ROS production induced by EAE and ameliorated clinical symptoms in rats. CAPE is also able to block glutamate-induced excitotoxicity, which has an important role in ischemia, by inhibiting phosphorylation of p38 and caspase-3 activation [9].

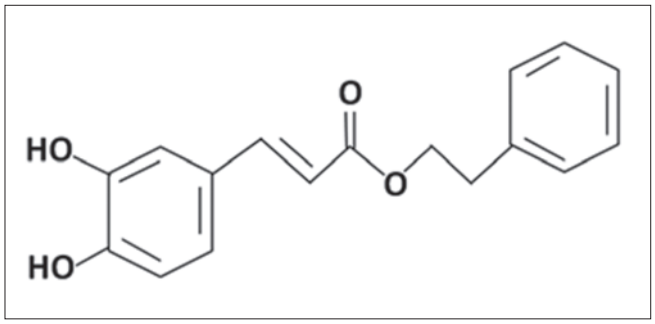

Figure 1: The structure of caffeic acid phenethyl ester

CONCLUSION

In order to emphasize the multi-faceted effects of CAPE, we would like the comments on the following: The clinical significance of CAPE arises not only from antioxidant, free radical scavenging, and direct neuroprotective activities, but also by strong NFκB, apoptosis, and NOS activity inhibitions, as well as inhibition of phosphorylation of p38, and caspase-3 activation.

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REFERENCES

1. Akyol S, Isik B, Altuntas A, Erden G, Cakmak O, Kursunlu SF, *et al.* Future opportunities in preventing ototoxicity: Caffeic acid phenethyl ester may be a candidate (Review). Mol Med Rep 2015 May 14. doi: 10.3892/mmr.2015.3785. [Epub ahead of print].
2. Akyol S, Akbas A, Butun I, Toktas M, Ozyurt H, Sahin S, *et al.* Caffeic acid phenethyl ester as a remedial agent for reproductive functions and oxidative stress-based pathologies of gonads. J Intercult Ethnopharmacol 2015;4:187-91.
3. dos Santos NA, Martins NM, Silva Rde B, Ferreira RS, Sisti FM, dos Santos AC. Caffeic acid phenethyl ester (CAPE) protects PC12 cells from MPP toxicity by inducing the expression of neuron-typical proteins. Neurotoxicology 2014;45:131-8.
4. Ilhan A, Iraz M, Gurel A, Armutcu F, Akyol O. Caffeic acid phenethyl ester exerts a neuroprotective effect on CNS against pentylenetetrazol-induced seizures in mice. Neurochem Res 2004;29:2287-92.
5. Sahin S, Sogut S, Ozyurt H, Uz E, Ilhan A, Akyol O. Tissue xanthine oxidase activity and nitric oxide levels after spinal cord ischemia/reperfusion injury in rabbits: Comparison of caffeic acid phenethyl ester (CAPE) and methylprednisolone. Neurosci Res Commun 2002;31:111-21.
6. Palluy O, Rigaud M. Nitric oxide induces cultured cortical neuron apoptosis. Neurosci Lett 1996;208:1-4.
7. Natarajan K, Singh S, Burke TR Jr, Grunberger D, Aggarwal BB. Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. Proc Natl Acad Sci U S A 1996;93:9090-5.
8. Ilhan A, Akyol O, Gurel A, Armutcu F, Iraz M, Oztas E. Protective effects of caffeic acid phenethyl ester against experimental allergic encephalomyelitis-induced oxidative stress in rats. Free Radic Biol Med 2004;37:386-94.
9. Wei X, Ma Z, Fontanilla CV, Zhao L, Xu ZC, Taggliabraci V, *et al.* Caffeic acid phenethyl ester prevents cerebellar granule neurons (CGNs) against glutamate-induced neurotoxicity. Neuroscience 2008;155:1098-105.

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