Propolis as a Complex Compound May Contain Many Active Ingredients Like Caffeic Acid Phenethyl Ester (CAPE)

To the Editor:

We have read with great interest the article "Propolis induced mania with psychotic features: A case report" by Ozcan et al. in Bulletin of Clinical Psychopharmacology[1]. The authors reported that high dose of propolis may have been the triggering factor of the manic symptoms with psychotic features. We would like to add some valuable information for both propolis and its active component, caffeic acid phenethyl ester (CAPE) (Figure 1) to explain why such type of symptoms might occur after propolis ingestion. For a better understanding of the cellular mechanisms of these potential psychiatric side effects, the authors should have mentioned the ingredients of propolis mixture, which have different physical, chemical, and functional properties.

Propolis has been used in folkloric medicine for centuries. The composition is very complex and contains commonly waxes, resin, and some volatiles. Propolis resin include phenolic acids, their esters, flavonoids (flavones, flavanones, flavonols, dihydroflavonols, and chalcones), terpenes, aromatic aldehydes and alcohols, fatty acids, stilbenes, and steroids[2]. Currently, there is no medically recommended dose for propolis and therefore more scientific studies are needed to reach a final decision on that specific topic. The origins of propolis products are so various that it is very difficult to reach a reliable decision and comprehensive results for dosing. Although there is no data on the toxicity of CAPE in vivo, propolis has a low order of acute oral toxicity with reported LD50 ranging from 2,000 to 7,300 mg/kg in mice[3].

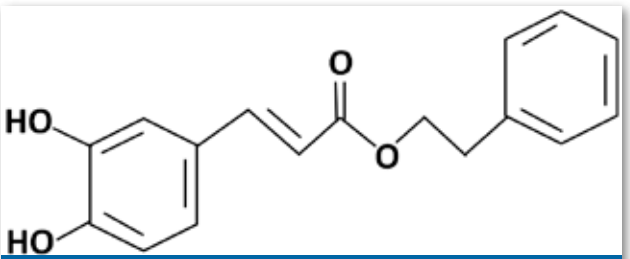

Figure 1: The structure of caffeic acid phenethyl ester (CAPE)

CAPE is the most commonly studied component of propolis. It strongly inhibits reactive oxygen species production in human neutrophils and in the xanthine/xanthine oxidase systems at 10 μM concentrations[2]. It effectively down-regulates a number of pro-inflammatory cytokines and inflammatory mediators by inhibiting NFκB[2]. The volume distribution values were ranged from 1,555 to 5,209 ml kg^{-1} decreasing with dose, and the elimination half-life was ranged from 21.2 to 26.7 min showing independence from the dose; so, CAPE was distributed extensively into the tissues and eliminated rapidly, indicating a high value of volume of distribution and similar short elimination half-life[4].

One of the most important pharmacological drawbacks of many compounds is their restricted passage through the blood-brain barrier (BBB), which in turn restricts their actions. It has been reported that CAPE can prevent hypoxic/ischemic-induced neonatal rat brain injury in the hippocampus, cortex, and thalamus since it can easily cross the BBB. Therefore, the possible responsible compound for the above-mentioned psychiatric symptoms might be CAPE. Although commercial propolis extracts include some ingredients that has been known safe compounds, some other propolis samples from unknown sources might have unknown pharmacological and toxicological effects. On the other hand, CAPE has been known as a neuroprotective agent (at pharmacological doses) on the CNS, which was shown in experimental studies such as penthylenetetrazol-induced seizures[5]. However, the effects of high doses cannot be estimated whether it is toxic or not.

In conclusion, every single bioactive constituents of propolis should have been studied to reach a reliable conclusion on the neuropsychiatric effects of propolis. Indeed, the studies should elaborate the molecular mechanisms and signaling pathways of each active propolis content. In this regard, we strongly believe that the complementary use of propolis for different purposes needs further attention in the daily practice of psychiatrists.

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Massive Creatine Kinase Elevation During Antipsychotic Drug Treatment with Olanzapine and Quetiapine

To the Editor,

Second-generation antipsychotics may lead to adverse events such as metabolic disorders, agranulocytosis or muscle damage, but massive elevations of serum creatine kinase (CK) in the absence of neuroleptic malignant syndrome (NMS) is a relatively uncommon side effect. Recently, raising awareness with this condition, the side effect was reported as a distinct clinical entity, 'a massive asymptomatic CK elevation' related to atypical antipsychotics[1].

A 19 year-old man was admitted with the diagnosis of bipolar disorder with complaints of increased energy, decreased need for sleep, unusual talkativeness, grandiosity, and racing thoughts. Two years ago, he was treated with olanzapine, 10 mg/day, for his first manic episode with abovementioned complaints for three days when he was noted to have extremely elevated CK in his routine laboratory testing; initial level of 17,024 IU/l up to 32,440 IU/l (normal:<200) during one week period (AST: 601 IU/l, ALT: 229 IU/l, LDH: 1278 IU/l, myoglobinuria:<21 ng/ml). The other routine laboratory tests including GGT level, thyroid functions, electrocardiography and abdominal ultrasonography were normal. Any other diagnostic criteria for NMS (hyperthermia, autonomic instability, altered mental status, severe muscular rigidity or leukocytosis) were not detected. Normalization of parameters during one month by discontinuation of olanzapine supported an antipsychotic-induced CK elevation. Then, he was discharged with quetiapine, 50 mg/day and thereafter 100 mg/day.

At his recent admission, aripiprazole 5 mg/day and quetiapine, 100 mg/day was given for his manic episode. Because of hypochondriasis, aripiprazole was ceased and lithium, 900 mg/day added and increased to