**Kratom and its Active Ingredients - Opioid or Not?**

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The growing opioid epidemic has challenged the scientific community not only about the challenges of identifying compounds with opioid-like characteristics, natural or synthetic, which carry addiction liabilities, finding treatment for opioid addicts, but also what to call some of the compounds that have become common sources of abuse. It must be taken very seriously what criteria scientists may use to classify or name compounds as the results of such endeavor could lead to criminality of the people who use or abuse those compounds.

The naming of biological/pharmacological compounds requires several considerations. To illustrate this point, let us consider hormones and in particular, estrogens. As a class there are basically three types based on composition: polypeptides (e.g. hypothalamic and pituitary hormones gonadotropic releasing hormone (GnRH) and pituitary luteinizing and follicle stimulating hormones (LH and FSH), aromatic amines (e.g. thyroid hormones thyroxine (T4) and triiodothyronine (T3)) and steroidal hormones like androgens (e.g. testosterone and androstenedione) and estrogens (e.g. estradiol). Hormones called estrogens have several common structural configurations and biological activities. Structurally, it must possess characteristics similar to 17β-estradiol (E2) - the most dominant and potent circulating female sex hormone in the non-pregnant female including (a) the steroid nucleus, derived from its precursor cholesterol, and (b) hydroxyl groups or other substitutions especially on carbons 3 (C3) and carbon 17 (C17) which are known to confer its biological potency (Figure 1a). Well known biological activities of E2 includes actions on the hypothalamic-pituitary ovarian axis to stimulate ovarian development and steroid production, prepare the endometrium for blastocyst implantation and the development of female secondary sex characteristics. A synthetic estrogen that was designed with the intention of approaching the potency of E2 was diethylstilbestrol (DES), a drug that possessed the crucial 2 hydroxyl groups on C3 and C17 and could therefore mimic E2 (Figure 1b) was used to prevent habitual abortions in the 1950s. With the disadvantage of not being able to be metabolized and therefore detoxified as E2 is, DES has been found to be teratogenic and carcinogenic [1]. Changes to the parent E2 structure produces very significant loss of biological effects, so that estrone (E1) - the primary circulating estrogen in a postmenopausal female, has only about 30% of the potency of E2. This is due primarily to the keto group substitution on C17 (Figure 1c). On the other hand, and as the name implies, estriol (E3), the primary estrogen in circulation in the pregnant female because of E2 metabolism by placental enzymes (and also a metabolite of estrone), has 3 hydroxyl groups at positions C3, C16α and C17β and with that a considerable loss of estrogenic potency (Figure 1d). The name estrogen is also conferred on compounds that can interact with classical estrogen receptors in estrogen responsive target tissues and produce effects that are characteristic of 17β-E2 (agonist, e.g. DES or a partial agonist like phytoestrogens) or opposite to estrogens (antagonist, e.g. clomiphene citrate). Structural modifications to the estradiol molecule produce such significant changes to the biological activities because they affect the binding affinity of the resulting compounds to the estrogen receptor. A complicating issue arises because of cross reactivity where structurally and non-structurally related compounds may be able to bind to target tissue receptors. Classical examples are the endocrine disruptors - xenobiotic compounds like the industrial plastic chemical Bisphenol A (BPA) (Figure 2a) and the pesticide dichlorodiphenyltrichloroethane (DDT) (Figure 2b) that can bind to the estrogen receptor and mimic estrogen responses. However, these compounds are not labeled estrogens.

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Figure 1: Structures of natural estrogens, available from the U.S. National Library of Medicine, PubChem Database [2].

Figure 2: Structures of select endocrine disruptors, Bisphenol A and p,p'-DDT, available from the U.S. National Library of Medicine, PubChem Database [2].
The Dietary Supplement and Health Education Act (DSHEA) of 1994 passed by the 103rd Congress of the United States made dietary supplements available to the general public with the primary intention of helping to improve the health status of its citizens. Currently more than 50% of the United States population ingest dietary supplements, which include vitamins and herbal products. The myth is that the United States government approves every over-the-counter dietary supplement. Because the burden actually lies with the Food and Drug Administration (FDA) to prove that a "supplement" is a danger health, sometimes it takes many years for the FDA to act. The "melting pot" metaphor is often used in the United States to describe the fusion of different nationalities and cultures in which people import habits, diets and holistic treatment, which may include the use of plant products. Such is the case now with the popular plant called kratom the use and abuse of which is now being hotly debated and calls upon the scientific community to classify it.

Kratom is the common name for *Mitragyna speciosa* a tropical tree of the Rubiaceae family which is indigenous to Malaysia, Thailand and parts of Africa where it is traditionally used as an analgesic (a substitute for opiates) stimulant, or for its mild euphoric effects [3]. Traditionally the leaves may be chewed by workers to increase energy while providing pain relief from muscle aches. There is also anecdotal evidence that kratom has been used to help with opioid and alcohol withdrawal symptoms. However, because of mounting reports of adverse events associated with kratom use the FDA banned the import of kratom in 2016 and the Drug Enforcement Administration (DEA) initially issued a notice of intent to classify the active ingredients in kratom, mitragynine and its metabolite 7-hydroxymitragynine (Figures 3a and 3b) as schedule 1 drugs [4]. This was later withdrawn.

**Figure 3:** Structures of select endocrine disruptors, Bisphenol A and p,p'-DDT, available from the U.S. National Library of Medicine, PubChem Database [2].

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In the United States, the Controlled Substances Act classifies a drug as Schedule 1 if it is deemed not to have medical use and has a high potential for abuse that could lead to severe psychological and physical dependence. In 2017 (and enforced later in 2018), the FDA commissioner posted statements regarding the presence of “opioid compounds” mitragynine and 7-hydroxymitragynine (7-OH-mitragynine), the latter being the most potent although present in smaller quantities in kratom. These compounds produce central nervous system effects mediated by high affinity binding to mu opioid receptors (MOR) as agonists, and the development of tolerance [5]. In making the scheduling recommendation to the DEA, the FDA recommended scheduling of the active ingredients and not *Mitragynine speciosa* itself. What that means is that manufacturers would be “free” to add the plant to several over the counter products.

In making their recommendations to the DEA, the FDA did not label the kratom active ingredients products as "opioid compounds" based on structure-activity relationship (SAR) a key to many aspects of drug discovery and identification [6] which is often the basis of naming compounds as opioids, but rather on biological effects, mediated by the binding of the active ingredients to the MOR.

In summary, it is still unresolved if the active ingredients in kratom are opioids and therefore should be considered a Schedule 1 drug, so as to restrict its availability. In my opinion, using the criteria that has been used for classifying several natural and synthetic biologically active compounds, they are not opioids but opioid-like.

**Bibliography**