Kratom-Drug Interaction I

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Kratom or Mitragyna speciosa (Korth.) Havil. is an indigenous plant of Malaysia and Thailand. Kratom leaves are used by some Malays and Thais for their opium- and coca-like stimulant effects (Takayama, 2004) to alleviate tiredness and increase tolerance of hard work under a scorching sun (Hassan et al., 2013). The primary active indole-based alkaloid of kratom is mitragynine (approximately 60% based on the crude alkaloids of kratom) (Maurer, 2010). Kratom has also been used as a folk medicine for common illnesses including coughing, diarrhea, muscle pain, hypertension, and to treat heroin addicts (Maurer, 2010). However, there are some side effects such as anorexia, dry-mouth, diuresis, and constipation. Withdrawal symptoms are experienced by users who have consumed kratom leaves for a long time. These symptoms include hostility, aggression, aching muscles and bones, jerky movements of the limbs, anorexia, weight loss, and insomnia (Suwanlert, 1975).

Kratom was classified in Category V of the Narcotic Act, B.E. 2522 (1979). In 2016, the Office of the Narcotics Control Board (ONCB) conducted a survey to estimate the size of substance abuse populations in southern Thailand. They found that kratom was the most popular substance abused, the second and third were boiled kratom leaves, and marijuana, respectively (Assanangkornchai et al., 2016). In the south of Thailand, kratom is not perceived as an illegal drug. It has a place in the traditional way of life. In this context, consumers usually chew fresh leaves or brew the leaves with hot water and drink as infusion. However, teenagers now drink a kratom cocktail known as 4 x 100, which is considered an addictive substance. The cocktail is a mixture of boiled kratom leaves with a cola drink, antitussive syrup, and, typically, coffee or codeine.

A drug interaction is a modification of the effects of one drug caused by the combination of another drug, herbal, or food products. The combination most frequently alters the pharmacokinetics or pharmacodynamics of the main drug. The interaction may cause adverse health effects or render the main drug ineffective in clinical use. Drug interactions are mainly caused by pharmacokinetic interactions. These interactions can occur during absorption, distribution, metabolism, and/or excretion, increasing or reducing drug concentrations in plasma. The main drug is likely to become toxic or sometimes subtherapeutic. They are produced by changes in absorption, distribution, metabolism or excretion due to co-administered drugs. Pharmokinetic interactions are detected by changes in pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), area under the curve (AUC) of plasma concentration versus time, volume of distribution (V_d), elimination half-life ($t_{1/2}$), and elimination rate constant (λz).

According to clinical pharmacology studies, most drug interactions involved metabolic processes, particularly the metabolism of drugs through CYP450 enzymes. There are several reports that kratom extracts inhibited human recombinant CYP450. The degree of inhibition was clarified by half-maximal inhibitory concentration (IC_{50}) values. Methanolic and alkaloid kratom extracts and mitragynine showed strong inhibitory activity against the CYP2D6 isoenzyme with IC_{50} values of 3.6 ± 0.1 µg/mL, 0.636 µg/mL, and 0.45 ± 0.33 µM, respectively. The alkaloid kratom extract exhibited competitive inhibition, while mitragynine showed non-competitive inhibition of the CYP2D6 isoenzyme. All kratom extracts also inhibited

other CYP450 isoenzymes (Table 1) (Hanapi et al., 2010; Kong et al., 2011; Ismail et al., 2013). Therefore, when co-administered, kratom may alter the pharmacokinetics of drugs that are catalyzed through CYP450 isoenzymes, such as the substrate of CYP2D6, CYP3A4, and CYP2C9, and might lead to drug interactions.

Table 1 Inhibitory effect of kratom extracts on CYP450

Kratom extracts	CYP450 isoenzymes	IC50 values	Ki values	Reference
Methanol extract	CYP2D6	3.6 ± 0.1 µg/mL	NA	Hanapi et al., 2010
	CYP3A4	142.8 ± 13.8 µg/mL		
	CYP2C9	NA		
Alkaloid extract	CYP2D6	0.636 µg/mL	2.6 µg/mL	Kong et al., 2011
	CYP3A4	0.78 µg/mL	1.526 µg/mL	
	CYP1A2	39 µg/mL	18.57 µg/mL	
	CYP2C19	NA	84.88 µg/mL	
Mitragynine	CYP2D6	0.45 ± 0.33 µM	12.86 µM	Ismail et al., 2013
	CYP3A4	41.32 ± 6.74 µM	379.18 µM	
	CYP2C9	9.70 ± 4.80 µM	155.80 µM	

Source : not applicable

Many studies and case reports have described pharmacokinetic interactions between kratom extracts and other drugs. A 27-year-old man with a past medical history of Asperger Syndrome, bipolar disorder, and substance abuse was found dead inside his secured residence. He was taken to hospital for a post-mortem examination in which a blood specimen was collected for toxicological assessment. Valproic acid and quetiapine were quantitatively positive at 8.8 µg/mL, and 12 µg/mL, respectively. Mitragynine was qualitatively positive. The presumed cause of death was seizures/convulsion. Quetiapine is known to be predominately metabolized in the liver by cytochrome P450 3A4 (CYP3A4). It may be that, in this case, the metabolism and clearance of quetiapine was affected by the inhibitory influence of mitragynine (Hughes, 2019) present due to the concomitant use of kratom. In addition, mitragynine and the alkaloid from kratom extract exhibited a toxicokinetic interaction with permethrin, which is a pyrethroid insecticide. Permethrin was detoxicated by hydrolysis via carboxylesterase to form inactive phenoxybenzylalcohol (PBALc) which was eliminated by CYP2D6, CYP3A4, and CYP2C9 enzymes (Kaneko, 2011). Mitragynine and alkaloid, kratom extract delayed the elimination of permethrin, inducing a long elimination half-life and decreasing the elimination rate constant (K_{el}). Therefore, the inhibition of permethrin metabolism and elimination due to mitragynine and alkaloid from kratom extract might cause permethrin toxicity. (Srichana, 2015).

Since the combination of kratom leaves and certain drugs may contribute to serious side effects, there is a need to increase awareness of herb-drug interactions that carry the risk of toxicity or render treatment ineffective. Pharmacokinetic and pharmacodynamic interactions must be taken into consideration and understanding. Knowing about mechanism of drug interactions and their causes may help to avoid them.

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