Original Article

Protein-Ligand Identification and *In Vitro* Inhibitory Effects of Cathine on 11 Major Human Drug Metabolizing Cytochrome P450s

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Abstract

Cathine is the stable form of cathinone, the major active compound found in khat (*Catha edulis Forsk*) plant. Khat was found to inhibit major phase I drug metabolizing cytochrome P450 (CYP) enzyme activities *in vitro* and *in vivo*. With the upsurge of khat consumption and the potential use of cathine to combat obesity, efforts should be channelled into understanding potential cathine-drug interactions, which have been rather limited. The present study aimed to assess CYPs activity and inhibition by cathine in a high-throughput *in vitro* fluorescence-based enzyme assay and molecular docking analysis to identify how cathine interacts within various CYPs' active sites. The half maximal inhibitory concentration (IC_{50}) values of cathine determined for CYP2A6 and CYP3A4 were 80 and 90 μM, while CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2 and CYP3A5 showed no significant inhibition. Furthermore, in K_i analysis, the Lineweaver-Burk plots depicted non-competitive mixed inhibition of cathine on both CYP2A6 and CYP3A4 with K_i value of 63 and 100 μM, respectively. Cathine showed negligible time-dependent inhibition on CYPs. Further, molecular docking studies showed that cathine was bound to CYP2A6 via hydrophobic, hydrogen and π-stacking interactions and formed hydrophobic and hydrogen bonds with active site residues in CYP3A4. Both molecular docking prediction and *in vitro* outcome are in agreement, granting more detailed insights for predicting CYPs metabolism besides the possible cathine-drug interactions. Cathine-drug interactions may occur with concomitant consumption of khat or cathine-containing products with medications metabolized by CYP2A6 and CYP3A4.

Keywords

cathine, CYP, *in vitro*, docking, herb-drug interaction

Introduction

Cathine (d-norpseudoephedrine (NPE)) is one of the major constituents found in the *Catha edulis Forsk* plant, which is also commonly known as khat.[1] Khat is a perennial shrub cultivated in khat-belt countries such as in Africa and the Middle East, that are ingested not to gain nutritive values but to attain psychostimulatory effects.[2] Khat was traditionally used in social gatherings in Yemen and widely cultivated as a source of income replacing coffee cultivation despite debates that khat cultivation drains foreign investment.[3] Khat chewing is a tradition in khat-belt countries with each khat sessions lasting 3 to 4 hours with 100-200 g of leaves chewed, which induces mild euphoria and excitation in its users.[4] In the early 1930s, Wolfes identified cathine (S,S(+)phenylpropanolamine) as norpseudoephedrine, which was one of the khat alkaloids that contribute to the pharmacological effects of khat leaves.[5] It was reported that in every 100 g of fresh khat, there were 36 mg of cathinone, 120 mg of cathine and 8 mg of norephedrine present.[5] Young stems and flowers of khat plants contain 1-phenyl-1,2-propanedione, cathinone, cathine and norephedrine.[6] Cathinone reductase present in khat was accountable for reducing cathinone to cathine in the presence of NADPH.[6] However, the quantity of cathine depends on the type of khat in which green khat contains a higher amount of cathine and norephedrine than red khat.[6] Besides khat plant,

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