

Drug–herb interaction through inhibition of cytochrome P450 alters the pharmacological response and/or toxicities of drug used concomitantly. In our screening, *Piper nigrum* L. was observed to inhibit cytochrome P450 2D6 (CYP2D6) in human liver microsomes. Thus, the MeOH extract of this plant was investigated for their chemical constituents and 19 alkaloids including a new pipericyclobutanamide were isolated. Their structures were elucidated on the basis of spectroscopic analyses. The isolated compounds were tested for their inhibition on human liver microsomal dextromethorphan *O*-demethylation activity, a selective marker for CYP2D6, and pipericyclobutanamide A (**17**) showed the most potent inhibition with an IC₅₀ value of 0.34 μ M. The result demonstrated the potential of drug–alkaloids interaction on concomitant consume of white pepper with the drugs being metabolized by CYP2D6.