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Biotransformation Study of Some Alkaloids and Synthetic Drugs Containing Pyridine or Piperidine Nucleus

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By

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ABSTRACT

Key words: Biotransformation, alkaloids, plant cell culture, mammalian metabolism, antiproliferative, cytotoxic, antioxidant, antimicrobial activity, LC-MS/MS and NMR.

The use of microbial models provides a number of merits, which makes it surpassing the *in-vivo* drug metabolic studies. Moreover, the expression of the most human liver cytochrome P450 families in microorganisms is effectively-utilized as a predictive tool for exploring the drug metabolism and providing a handy tool for carrying out subsequent biological and toxicological evaluation of the produced metabolites.

The metabolic fate of the studied alkaloids and synthetic compounds containing pyridine or piperidine nucleus, which are nicotine, ricinine, chlorpheniramine, piperine, pelletierine and cyproheptadine, were investigated using the biocatalytic systems of some plant and microbial cultures.

Experimental protocols:

An initial microbial screening protocol was adopted using twenty four microbes to select the highly effective strains in biotransforming each drug. A scale-up fermentation procedure was employed for the sake of production of substantial amounts of the drug metabolites to be used in the structural elucidation and biological evaluation. The characterization of the isolated metabolites was carried out using different spectroscopic techniques such as IR, UV, ESI-MS/MS, ^{1}H- and ^{13}C NMR spectroscopy.

The biological activities of the identified metabolites were explored. Screening of the lympho-proliferative, anticancer and antimicrobial activities of the metabolites, in addition to their antioxidative capacity was carried out.

Furthermore, the bioconversion efficiency of some established plant cultures towards the studied drugs was investigated and the bioransformation products were identified by LC-MS/MS analysis.

Results:

The current study presented several microbial models for the mammalian metabolism of the investigated drugs. A wide variety of metabolic reactions was observed, such as *N*-oxidation which was accomplished by *C. elegans* in metabolizing nicotine and chlorpheniramine into their *N*-oxide derivatives. Whereas, C-oxidative metabolism was accomplished by *A. niger* in the metabolism of cyproheptadine into a hydroxylated metabolite. Furthermore, O-dealkylation was discerned in the cleavage of the methylene-dioxy ring of piperine accomplished by the culture of *S. cerevisiae*. The latter was also efficient in achieving oxidative deamination of chlorpheniramine to 3-(p-chlorobenzyl)-3-(2-pyridyl)-propanol. On the other hand, a reduction followed by a dehydration reaction was demonstrated in the metabolism of pelletierine by *A. flavus* into 2-propenyl-2-piperidine.

N-demethylation metabolic reaction was demonstrated in the metabolism of nicotine by *S. platensis* (followed by a dehydrogenation reaction) and the metabolism of cyproheptadine by *A. niger* (accompanied by *N*-hydroxylation reaction). However, lactam formation was only observed in the metabolism of pelletierine by two yeast species: *R. rubra* and *S. cerevisiae*.

The obtained metabolites showed a diverese biological activities such as: **(a)**-stimulant effect on PBMCs proliferation as demonstrated by met-4, met-9 and met-10, **(b)**-anticancer activity was exhibited by met-9, met-10 and met-13, **(c)**-antibacterial activity was displayed by met-9 and met-10, and **(d)**-antioxidant capacity was revealed by met-10 and met-13.

Lastly, the tested plant cell cultures were proven to be qualitatively competent to the microbial biocatalytic systems in accomplishing some of the previously mentioned metabolic reactions when their cultures were inoculated by the investigated drugs.

Furthermore, there was a parallelism observed between the metabolic fate of the studied drugs using both the microbial and plant culture biocatalytic systems.