Metabolism of diallyl disulfide, isolated from garlic, by rat liver microsomes

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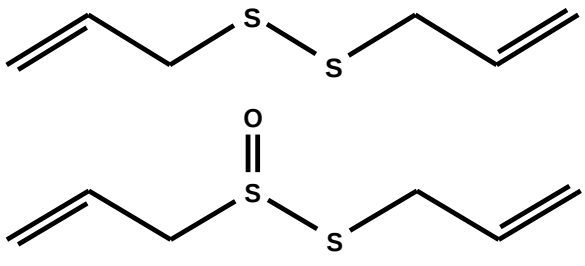
Many cancerogenesis studies have pointed out the chemoprotective effects of garlic. DADS (diallyl disulfide), a flavour compound of garlic, has been shown to protect liver from carcinogenesis induced by various chemicals (1, 2).

We have studied *in vitro* the metabolism of diallyl disulfide (DADS) by rat liver microsomes in presence of NAPDH. Only one metabolite has been separated by HPLC and identified by diode array detection using synthetic reference compound. This metabolite is allicin (DADSO or diallyl thiosulfinate) which corresponded to the oxidation of DADS. No other product was detected whereas in the same conditions Brady *et al*. demonstrated that the diallyl sulfide (DAS), another compound of garlic, is successively oxydated in DASO and DASO2 (3).

The transformation of DADS involved the cytochrome P450 monooxygenases (CYP), the most important drug metabolising enzymes. The CYP are divided in family and subfamily with respect of sequence homology. We have identified the P450 isoenzymes involved in this transformation by induction of liver microsomes which modify the proportion of each isoenzyme. Phenobarbital or DADS (inducers of the CYP2B family) enhanced the rate of formation of the DADSO whereas clofibrate (CYP4A), acetone (CYP2E1) or dexamethazone (CYP3A) decreased it. Methylcholanthrene (CYP1A) has no effect. The effects of chemical inhibitors of CYP were also analysed with non-induced and induced microsomes. Metyrapone (specific of CYP2B) and alpha-naphtoflavone (CYP1A) exhibited the highest rate of inhibition with the corresponding induced forms. These results suggested the implication of CYP1A and CYP2B in the DADS metabolism.

The catalytic constants were determined with phenobarbital-induced microsomes and with non-induced microsomes.

The knowledge of DADSO as oxydated product of DADS is an important result as DADSO was often proposed to be the healthy active molecule of garlic.



DADS

DADSO

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(2) Haber-Mignard D., Suschetet M., Bergès R., Astorg P. and Siess M.H. (1996) Inhibition of aflatoxin B1- and N-Nitrosodiethylamine-induced liver preneoplastic foci in rats fed naturally occuring allyl sulfides. *Nutrition and Cancer* **25**, 61-70.

(3) Brady J.F., Ishizaki H., Fukuto J.M., Lin M.C., Fadel A., Gapac J.M. and Yang C.S. (1991) Inhibition of cytochrome P-450 2E1 by diallyl sulfide and its metabolites. *Chemical Research in Toxicology* **4**, 642-647.