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Preclinical Evaluation of Safety of Fucoidan Extracts From *Undaria pinnatifida* and *Fucus vesiculosus* for Use in Cancer Treatment

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Dear Editor:

We read with great interest the article by Mathew et al evaluating the potential metabolic drug-drug interactions with fucoidan from *Undaria pinnatifida* and *Fucus vesiculosus*.[1] Phase I as well as phase II enzymes activities have been assessed for inhibition and induction effects of *Undaria pinnatifida* and *Fucus vesiculosus* extracts.

Induction experiments of cytochromes P450 (CYP) were performed on cryopreserved human hepatocytes using a cocktail of specific probe drugs in the presence of rifampicin, a potent inducer of multiple enzymes. As stated in the phase I enzymes induction assays methods section, the cocktail of probe drugs was composed of "dextromethorphan for CYP2C8/2C9, diclofenac for CYP2D6, and docetaxel for CYP3A4."

First of all, it is widely accepted that CYP2D6 is not inducible.[2] Induction experiments for CYP2D6 are therefore not required for new chemical entities by the regulatory agencies. Recently, an article published by Farooq et al[3] indicating a potential induction of CYP2D6 by corticosteroids has been withdrawn because of a retraction of the authors as they were unable to reproduce the results.[4]

Second, there is confusion in the association between the probe drugs that were used and their related metabolic pathways. In fact, dextromethorphan is a specific probe drug for CYP2D6 (FDA [Food Drug Administration] guidance), diclofenac for CYP2C9 (FDA guidance), and docetaxel for CYP 3A4/5.[5] Dextromethorphan is mainly metabolized to dextrorphan by CYP2D6, and to a lesser extent to 3-methoxymorphinan by CYP3A4/5.[6] Diclofenac is metabolized to 4′-hydroxy-diclofenac by CYP2C9[7] and docetaxel is metabolized to hydroxydocetaxel by CYP3A4/5.[8]

Third, there is no specific probe drug for CYP2C8 in the used cocktail. The validated probe drugs for this enzyme are paclitaxel, amodiaquine (FDA guidance), repaglinide, montelukast, and pioglitazone.[9] Therefore, any reference to CYP2C8 in the article should be interpreted with caution.

Finally, in the CYP inhibition assays, only 2 substrates (dibenzylfluorescein and 3-(2-(N,N-diethyl-Nmethylammonium)ethyl)-7-methoxy-4-methylcoumarin iodide) were used as substrates for CYP2C8, CYP2C9, CYP3A4/5, and CYP2D6 without giving any explanation about the metabolic pathways and the specificity regarding the 4 enzymes. As dibenzylfluorescein is a substrate of CYP 2C9, 2C8, and to a lower extent of CYP 3A4[10] and 3-(2-(N,N-diethyl-N-methylammonium)ethyl)-7-methoxy-4-methylcoumarin iodide is specific to CYP 2D6.[10,11] Moreover, Reference 11 in the article[12] is not related to this assay at all.

Therefore, conclusions from the present article should be interpreted with great caution and should not be translated into any clinical interpretation.

Declaration of Conflicting Interests

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