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LETTER TO EDITOR – ASSESSMENT OF ACUTE AND SUB-ACUTE TOXICITY OF OLIVE POMACE IN FEMALE WISTAR RATS

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Dear Editor,

We read with interest the paper by Badi et al[1] recently published in *World Cancer Research Journal*, which considered the toxicological profile of Olive Pomace (OP) extract in Wistar rats.

It has been demonstrated that OP represents a relevant source of phenolic molecules, with several biological properties, such as anti-ulcer, gastroprotective, hepatoprotective, anti-diabetic and hypolipidemic, as well as anti-HIV, anti-inflammatory, immunoregulatory, and even anticancer activities[2].

In recent decades, the use of complementary and alternative medicine (CAM) has been introduced also for cancer treatment[3,4]. CAM consists of medical procedures, other than standard medical care, aimed to improve life's quality of patients, thus controlling symptoms and alleviating side effects of ongoing therapies. Within CAM, herbal product intake is one of the main measures adopted by cancer patients[5-8]. However, the main issues related to the administration of natural compounds are the occurrence of adverse effects and possible interactions with standard chemotherapy. For these reasons, we believe that toxicity studies on these molecules of natural origin are fundamental to avoid severe adverse reactions in cancer patients.

Badi et al[1] evaluated the possible acute and chronic toxicological effects of OP methanol extract in animal models. Acute toxicity results demonstrated that this natural extract is safe for rats after 14 days of treatment at all doses tested (200 – 5000 mg/kg, by gavage). A lower dose range (3.12 – 500 mg/kg, by gavage) was tested for sub-acute toxicity evaluation: following 28 days of administration of OP extract, rats showed no relevant changes compared to the control, thus confirming a relative safety of the product. Some hematological and biochemical parameters, however, appeared to be altered; a significant change of animal body weight was observed as well[1]. These results suggested that OP extract has a potential of use in anticancer formulations according to its acute and sub-acute safety profile. However, additional chronic toxicological studies are needed to validate the safe dosage[1].

As mentioned above, CAM includes the use of herbal products, comprising those used in Chinese medicine or homeopathic formulations. Despite the huge clinical application of natural compounds, there is still concern about their safety due to shortage of toxicological studies reported in the literature. Moreover, another aspect to take into account is represented by gender, considering that sex differences can influence pharmacokinetic and pharmacodynamic responses[9]. Toxicological investigations on animal models could predict the effect of natural molecules on several organs, such as the liver, kidneys, as well as reproductive system.

Furthermore, it is also important to determine the exact phytochemical composition of herbal products, as done by Badi et al[1] in their work. Indeed, it is not rare that substitution or adulteration of original plant processes are used to both enhance the product's potency and reduce pro-

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duction costs. Considering that the therapeutic effect of natural compounds is strictly related to the quantity and quality of their chemical phytoconstituents, the phytochemical analysis should always be reported[10]. On the other side, the toxicological knowledge of both plant extracts and their phytochemical composition is helpful to prevent adverse reactions in patients. Animal models, such as Wistar rats, allow the prediction of the safety profile of herbal products. Moreover, zebrafish and *Drosophila melanogaster* organisms are used for drug screening thanks to the advantageous drug delivery and low-cost[11-13]. Currently, *Drosophila melanogaster* offers genetic and molecular tools exploitable to determine the toxicity potential of drugs in male reproductive organs[14]. However, these types of studies implicate the use of several animals, thus recently various alternative models have been proposed to replace *in vivo* research and evaluate the development and the reproductive toxicities. Embryonic stem cells are used for development studies, while *in vitro* and *ex vivo* models for reproductive system research are still not established. Further studies will be necessary to develop alternative *in vitro* and *ex vivo* models exploitable for establishing the safety profile of herbal products[15].

We strongly encourage toxicological studies on naturally derived products, because such investigations are fundamental to assess the range of appropriate doses. In fact, the evaluation of side effects is the preliminary step to consider for developing new formulations aimed to be translated into clinical trials.

Conflict of interest:

The authors have no conflict of interest to declare

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