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COMMENTARY

Response to a comment by Luigi Cervo and Valter Torri on: "Dose–effect study of *Gelsemium sempervirens* in high dilutions on anxiety-related responses in mice" (Magnani P. et al., *Psychopharmacology*, 2010)

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Dear Editor,

We are glad that our *Psychopharmacology* paper, published on May 2010, is still raising interest with promise of a large impact. As a result of a challenging and pioneering work on this medicinal plant, we published three papers that do nothing more than report and discuss the experimental findings, as these were consecutively obtained. These papers contain all the necessary explanations, so that an unbiased perusal of them should be enough to confirm the overall validity of our findings. In the limited space at our disposal, we are forced to respond to only a few key points (a detailed rebuttal of the letter is available on request). The charge of non-reproducibility by Cervo and Torri is unfounded because in both series of experiments *Gelsemium sempervirens* worked in two well-validated models to the same direction, even with different statistical significance. In the cited preliminary study, we report the significant effects of *G. sempervirens* 5C, 7C and 30C in an open field (OF), and the *Psychopharmacology* paper reports a similar result, albeit with lower statistical significance ($p=0.060$, Fig. 2). In light–dark test (LD), the anxiolytic-like effect of *G. sempervirens* was highly significant in the second paper, while in the first one, it was present in 5C and 30C, albeit in a non-significant way. The differences may be due to the variability of animal responses, well known in behavioural research, and to some changes in protocols (animal vendor, type of housing in cages and sequence of tests) that we describe in the paper and in the cited review, as recognised also by Cervo and Torri. For further confirmation, we also performed a pooled analysis of the two papers' results and found a highly significant effect of *G. sempervirens* 5C, 7C and 30C in OF parameters (permanence in centre area) and of *G. sempervirens* 5C, 9C and 30C in LD parameters (time spent in light and number of light–dark transitions) (Bellavite et al. 2011). Regarding the lack of activity of buspirone and diazepam in OF parameters, as reported also by others (references in the *Psychopharmacology* discussion), this may suggest that the effect of *G. sempervirens* in OF concerns the exploratory behaviour and the decrease in neophobia, instead of the anxiolytic-like effect. *G. sempervirens* reproducibly did not alter the locomotion assessed in OF in any series, indicating that the effect was not sedative. The analysis of variance (ANOVA) was conducted appropriately since we compared each treatment group, composed of 48 mice, against 96 untreated mice in order to have a larger control group, and this is correct. In the ANOVA, the usual procedure is for each treatment group to be compared with a single control group, which is what we did. Comparing each treatment with each of the two controls would have engendered more problems of multiple comparisons for no useful purpose and resulted in loss of power.

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Moreover, the two control groups showed similar variability and could therefore be pooled without qualms. For what concerns the alleged lack of a dose–response effect, this is not at all uncommon in behavioural pharmacology and there can be a host of possible reasons. The objection arises from a misunderstanding of high-dilution effects and hormesis, where non-linear phenomena and possible physicochemical changes of the solvent come into play, as discussed and referenced in the paper (page 542, paragraph 3). These are not "post hoc" interpretations but rather up-to-date working models (Bellavite et al. 2010). This criticism is therefore also unjustified. Our research has reported for the first time the effect of *G. sempervirens* on two highly validated behavioural paradigms in laboratory mouse.

Yours sincerely,

Bellavite et al.

Conflict of interest The authors declare no conflict of interest.

References

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