

Report on the ‘Study of the inhibitory (toxic) effect of the alkaloids from chosen plants of Amaryllidaceae family on some human enzymatic systems (*in vitro* study) II’

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A detailed study was made of the alkaloidal content and biological activity of *Nerine bowdenii*, family Amaryllidaceae, a plant chosen because previous studies had shown this species to be a rich source of alkaloids. Twenty-one alkaloids were isolated and characterized, mainly from mass spectrometric and spectroscopic data; two of the isolated compounds were novel. When the compound was isolated in sufficient quantity it was tested for its ability to inhibit the activity of human cholinesterase, human butyrylcholinesterase, prolyl oligopeptidase and GSK-3 β , as well as for its cytotoxicity. The two most potent acetylcholinesterase inhibitory alkaloids in this study were undulatine and powelline, but in comparison with galanthamine, the standard drug, the levels of activity were quite low. Only 4'-*O*-demethylbelladine showed a significant inhibitory effect on butyrylcholinesterase.

In the prolyl oligopeptidase inhibition assay, seven of the tested alkaloids produced IC₅₀ values of less than 1 μ M. Of the compounds assayed for their cytotoxicity only two, haemanthamine and buphanisine, demonstrated significant activity.

Although the biological activities of the most potent substances tested in this study were not sufficiently high to put them into contention as potential medicinal agents, the results are of considerable interest and add significantly to the knowledge of the Amaryllidaceae alkaloids and their activities. The results obtained form the basis of several good research publications in peer-reviewed journals.

The thesis is logically presented and easy to follow. The Introduction gives a good background to the work. The various Amaryllidaceae alkaloids are introduced, their chemical structures presented and their known biological activities described. The methodology used was highly appropriate for the study, which was to be expected in view of the considerable experience and

success of the ADINACO research group in the field of Amaryllidaceae alkaloids. The results are clearly presented and the data discussed in a satisfactory way. The literature cited is appropriate and up to date.

As mentioned above, several research publications have resulted from this work and this is a good measure of the success of the study. In my opinion, the work presented is of the standard expected for the degree of PhD and I would certainly recommend that this award be granted.

Questions that I should like to pose are:

1. On page 7, it is stated that 'the Amaryllidaceae alkaloids are exclusively produced by plants in that family'. However, on page 14 it is stated that 'Amaryllidaceae alkaloids are largely restricted to the family Amaryllidaceae'. Are they or are they not found in other families?
2. Galanthamine is used in the treatment of patients in the early stages of Alzheimer's disease. In view of the range of activities recorded for various Amaryllidaceae alkaloids, are there any adverse side effects with the use of galanthamine in the treatment of Alzheimer's disease?
3. In view of your cytotoxicity results, how would you like to take this work forward?

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11.9.2018