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REVIEW

of PhD thesis of MSc Yang Yi

„Quantum chemical studies of selected compounds determined as active components of Traditional Chinese Medicine"

title in Polish:

„Kwantowo-chemiczne badania wybranych związków stanowiących aktywne komponenty w tradycyjnej medycynie chińskiej"

realized under supervision of Professor Szczepan Roszak
Faculty of Chemistry, Wroclaw University of Science and Technology

The PhD thesis presented by MSc Yang Yi is a fruitful combination of experimental NMR measurements and theoretical quantum chemical calculations which led to interesting results. As PhD Candidate indicated the aim of her studies were:

„*reliable theoretical studies of chemical properties of active components of Rheum palmatum and Radix puerarie plants. The antioxidative properties, related to radicals originating from active substances, are studied due to their importance in biological mechanisms. The experimental NMR measurements enhanced by theoretical predictions were performed as a potential source of descriptors for structure-activity endeavours. (…) The theoretical studies offer a new approach to TCM"* (Traditional Chinese Medicine) *„by the use of modern scientific technology.*"

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The PhD thesis was presented in English together with abstracts in Polish and Chinese and had 103 numbered pages. In the first and the second chapter the PhD Candidate interestingly introduced a reader to ideas of the Traditional Chinese Medicine (TCM) and craftfully connected them with the Western-European approach to utilizing pure chemical substances of well established activity in the drug formulation and in the therapy. She pointed to antioxidants present in radixes of *Rheum palmatum* and *Pueraria montana* – plants that are often used in numerous preparations in Traditional Chinese Medicine.

The PhD Candidate introduces us with compounds with anthraquinone core (dantron, emodin, aloe-emodin, rhein, chrysophanol, physcion, mitoxantron, daunorubicin) or those with isoflavone core (daidzein, daidzin, genistein, genistin, puerarin, formononetin). In Chapter 2 the PhD Candidate presents vitamin E and melatonin. Although the earlier concise introduction sketched the background of the scientific problem, the reasons why on 1 and ½ pages (Chapter 2) she presented information of these two arbitrary selected antioxidants is unclear.

In the next chapter the PhD Candidate formulated the main aim of the dissertation that is quantum chemical calculations on active compounds from *Rheum palmatum* and *Pueraria montana* plants in the context of their antioxidant properties. The experimental NMR measurements and results from computational studies should help in deriving molecular descriptors with potential utility in structure-activity endeavors, further enhanced by the initial studies on the intercalation of the selected active compounds into DNA fragments. With enthusiasm she highlighted the possibility of using quantum mechanics to study Traditional Chinese Medicine.

In Chapters 4 and 5 the PhD Candidate presented briefly theoretical and experimental methods used in her studies. She started with de Broglie's hypothesis and Schrödinger equation and finished with detailed information on computational DFT methods and basis sets used in her studies. Then she introduced readers to experimental NMR measurements and finally indicated which spectrometers were used in collecting signals.

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In Chapter 6 the PhD Candidate presented selected bond lengths of the 'representative' molecules and the corresponding radicals. She visualized HOMO, HOMO-1, HOMO-2 orbitals and discussed NBO derived atomic charges. These data triggered my question why in the Tables data for only 'representative' molecules were presented? – not for all molecules studied? Additionally, in the subchapter 6.1.1 we could find information that the results were obtained at B3LYP/aug-cc-pVTZ level, but in the subchapter 6.1.2 the info about computational level could not be found.

The results on anti-oxidative properties of the selected compounds are particularly interesting. The PhD Candidate showed that the bond dissociation enthalpy in the case of O-H bond connected the the C3 atom was about 375 kJ/mol which agreed well with the data from literature (371 kJ/mol). Moreover, it was even lower than the values for daunorubicin and mitoxantrone. The PhD Candidate calculated the change in Gibbs free energy for the reaction of hydrogen atom transfer from emodin to OH radical as equaled to -114.05 kJ/mol, suggesting high potential for the $OH^{\bullet}$ scavenging. Could, the PhD Candidate present during her public defense how she calculated ΔG values and at which temperature.

In my opinion the part of the dissertation concerning NMR measurements and the corresponding calculations based on Density Functional Theory is very interesting. The PhD Candidate showed that chemical shifts and shielding constants recorded experimentally and calculated at DFT level correlated very well for emodin, daidzein, and puerarin. To my disappointment there is no data for other molecules. - why?

In order to achieve the ambitious aims of her thesis the PhD Candidate carefully used appropriate quantum mechanical methods and performed NMR measurements. The calculations were carried out with the use of popular DFT functionals: B3LYP, M06-2X, PBE1PBE in connection with 6-311G(2d,2p) and aug-cc-pVTZ basis sets. To assess the effects of aqueous solution Polarizable Continuum Model was employed. Comparison of results obtained with different methods deserves approval, I would like to ask PhD Candidate to critically compare during the public defense:

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(i) basis sets 6-311G(2d,2p) and aug-cc-pVTZ

(ii) two selected functionals (from those mentioned above)

Additionally, please explain, how you selected computational methods for geometry optimization of the molecules.

Thanks to the quantum chemical studies the PhD Candidate successfully explained anti-oxidative properties of the plants *Rheum palmatum* and *Pueraria montana* used in Traditional Chinese Medicine, showing that active compounds present in these plants possessed ability to direct hydrogen atom transfer to highly reactive OH radical – thus acting as free radical scavenger. Moreover, it was shown that experimentally measured NMR chemical shifts were mapped very well with theoretical DFT calculations. The thesis presented by Yang Yi, despite minor shortcomings, is interestingly written and proves that the PhD Candidate understands scientific problems very well.

As to the minor issues in Figure 7 (and 8) two chemical structures (a) and (b) are presented but in the figure caption it is not clear which structure is which. In Figures 19 and 20 instead of PBE1PBE the acronym PBE0 should be used as it was in Table 10. In the page 60 instead of 6-31G(2d,2p) should be 6-311G(2d,2p) as indicated below and in computational details. One should provide references to scientific literature when stating that a particular functionals are being preferred by scientists (p.60).

Nevertheless, the PhD Candidate demonstrated that she understands well and uses skillfully various computational methods, bravely formulates scientific hypotheses and verifies them rigorously. Therefore the general knowledge of PhD Candidate in chemistry should be assessed highly favorably. It must be also highlighted that the results presented by Yang Yi had already been assessed by the referees appointed

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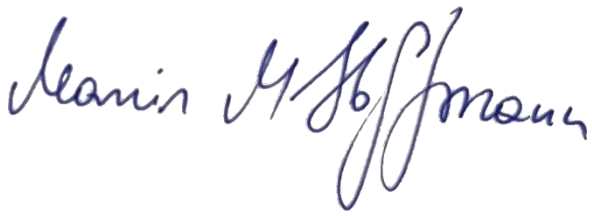
by the editors of scientific journals. Therefore the scientific achievements of Yang Yi had already been assessed by many experts.

Final assessment

All in all, I assess the PhD thesis presented by MSc Yang Yi highly favorably. Taking into account sound scientific results, successful combination of theoretical calculations and experimental measurements, as well as potential for applications I must state that the thesis presented by Yang Yi is an important contribution to our knowledge in chemistry. In my opinion the presented dissertation fulfills the statutory and customary requirements for PhD theses, constitutes original solution to the scientific problem, presents general theoretical knowledge of the PhD Candidate in chemistry and demonstrates the ability for independent scientific work. Therefore, I am recommending – to the Scientific Council of the Faculty of Chemistry of the Wrocław University of Science and Technology – admittance of MSc Yang Yi to the next stages of the doctoral process. In addition – taking into account interesting publication achievements of the PhD Candidate and original combination of Traditional Chinese Medicine with modern quantum chemistry – I suggest to award Yang Yi with PhD degree with distinction.



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