

## Reviewer's opinion of the doctoral dissertation

### SCREENING OF NOVEL CHELATORS OF MICROBIOGENIC METALS

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Opponent: Prof. Radomír Hrdina, MD, CSc.

#### 1. General characteristics

The submitted dissertation written in English by Maria Carmen Catapano, MSc "Screening of Novel Chelators of Microbiogenic Metals" has the structure of a commented set of 7 original works published in journals with impact factor (IF) in a total of 144 pages excluding embedded published works. It has a structure of this type of dissertation, i.e. abstracts in English and Czech are followed by introduction and theoretical part, list of abbreviations, aims of the dissertation, embedded copies of original published works, discussion, list of references, list of figures and tables and author's active participation in conferences.

It is worth mentioning that the dissertation has been developed in 2016-2020 as a part of a long-term research conducted at the Faculty of Pharmacy of Charles University in Hradec Králové, Department of Pharmacology and Toxicology, namely the Research Group of Cardiovascular and Respiratory Pharmacology and Toxicology under the leadership of Ass. Prof. Přemysl Mladěnka, Ph.D. and in co-operation with Ass. Prof. Laura Mercolini (University of Bologna).

#### 2. Theoretical part

The theoretical part is written on 32 pages, it is based on 157 references, logically structured. It deals with essential trace elements, namely iron, copper and zinc and their role in the organism including pathological states (inadequate concentration or conversely oversaturation with these elements). It also describes basic chelators, some of which are used

primarily in the intoxication (both acute and chronic) of the organism by the mentioned metals.

I think that in theoretical part should have been mentioned the studied chelators (also in Chapter 4: Aims of the work, see below): isoquercitrin and its iron and copper complexes at various pH, 4-methylcoumarins and copper chelation activity and the interaction of isoflavonoid metabolites with copper and zinc (mentioned in Abstract, p. 8).

### **3. Aims of dissertation**

Aims of the dissertation are mentioned very briefly and ambiguously. Eg. the term „different compounds“ is of little meaningful. In the paragraph above (see also Abstract, p. 8) is much more detailed description both chelating properties of the studied drugs and also development of novel methods for screening of metal chelation.

### **4. Evaluation of the achieved results**

M.C. Catapano, MSc has achieved original results in her work, the majority of which have been published in IF journals (see also 7 Assessment of Publication Activity). Here are some examples:

- isoquercetin is a moderately active ferrous, ferric and cupric chelator
- *o*- dihydrocoumarines are moderately active cupric, but not cuprous ions
- a new rapid and precise method for analysis of zinc chelation was developed
- an original method (HPLC-ED) was optimized for monitoring of •OH production by Fenton's reaction
- the first analysis the complex interactions of silymarin flavolignans with iron and copper

### **5. Author's contribution to the published papers, discussion**

Both chapters (pp. 124, 126-132, resp.) are characterized by consistency, the results achieved are critically confronted with literary sources. The author discusses unclear findings and suggests further possibilities of study in this area. These characteristics are therefore typical for a solid discussion.

### **6. Formal assessment**

Formally, the submitted work is logically structured, clear (apart from the above-mentioned remarks concerning part 3), comprehensible, written in good English, virtually free

of grammar or spelling mistakes. Here are some *formal details*: Title of dissertation (and elsewhere) – the term „microbiogenic“ is not found in any English dictionaries, (essential) trace elements would be correct; p. 19, last paragraph – Fe<sup>2+</sup> should be written with upper index Fe<sup>2+</sup>; figures and tables (p. 143) should have number of page where they occur. *Content comments*: p. 30 – a role of Zn ions in formulation complexes with insulin should be mentioned; p. 34 – excretion of iron from organism is not due to exfoliation of all mucosal surfaces but preferentially by digestive tract mucosa; p. 38: how is deferoxamine prepared?; p. 40 – why dimercaprol is called as British anti-lewisite (BAL)?

## **7. Assessment of publication activity**

7 original publications included in the dissertation were published in IF journals (range 2.895-4.180). In four publications, the applicant is the first author. All publications had undergone a rigorous review process, which speaks for itself. In addition, M. Catapano is co-author of one publication in the IF journal that is not directly related to the topic of the dissertation. Moreover, she actively participated in 4 domestic and foreign conferences.

## **8. Conclusion**

The results presented in the dissertation of *Maria Carmen Catapano, MSc* “Screening of Novel Chelators of Microbiogenic Metals” proved the ability of the applicant to research independently, which is also clearly documented by publication activity.

I strongly recommend the submitted dissertation for defense as a basis for the awarding of the Ph.D. pursuant to Section 47 (part 5) of the Higher Education Act (No. 111/1998 Coll.) after a successful defense.

24. 01. 2020, Hradec Králové (The Czech Republic)

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prof. MUDr. Radomír Hrdina, CSc.  
opponent