



**CHARLES UNIVERSITY**  
**Faculty of Pharmacy**  
**in Hradec Králové**

**DISSERTATION THESIS REVIEW**

submitted to the Faculty of Pharmacy in Hradec Králové, Charles University

**TITLE:** Differences in hemocoagulation in patients with metabolic disorders

**AUTHOR:** Jaka Fadraersada, M.Sc

**SUPERVISOR:** Prof. Přemysl Mladěnka, Pharm.D., Ph.D.

**CONSULTANT:** Alejandro Carazo, Pharm.D., Ph.D.

The dissertation thesis by Jaka Fadraersada, M.Sc. was focused on testing of two factor Xa inhibitors (FXa-Is) (xabans; rivaroxaban and apixaban) and two direct thrombin inhibitors (DTIs) (gatrans; dabigatran and argatroban), in both in healthy individuals and patients with familial hypercholesterolemia (FH) or type 1 diabetes mellitus (DMT1). Moreover, they aimed to investigate the correlation of coagulation values with anthropological and biochemical parameters from healthy individuals and patients, and to discover possible novel anticoagulant scaffolds (s). The thesis is well written on 128 pages, most of them related to the result section with 186 references. There are 8 tables and 56 figures.

The thesis's theoretical part focuses on describing coagulation pathways, DMT1, and familial hypercholesterolemia. This part is relatively short but clear to the reviewer. Maybe more pictures and schemes could have been used in this part. Moreover, the author is focused on the assessment of coagulation and clinically used anticoagulants. This chapter is nicely written and documented with appropriate pictures or schemes. The methodological part is sufficiently described, including the substances that were used.

The results section is documented by many figures showing the correlations of various metabolic parameters and tested coagulation methods. I would suggest or prefer that a short comment about the impact or importance of the results would be in this part in order to help readers to understand the figures better especially in healthy donors.

In general, I do appreciate the important topic of this thesis and its relation to two pathological conditions that might be rare (familial hypercholesterolemia) or autoimmune (DMT1). Despite the limitations of the *ex vivo* approach, the thesis brings interesting data that should definitely be evaluated by the *in vivo* approach.

This thesis presents interesting and important results with potential clinical impact that have been obtained in the framework of consistent experimental studies. Jaka Fadraersada, M.Sc., has proven herself to be a full-fledged scientist who is able to design and conduct experiments and present the collected data attractively and clearly.

**The thesis fulfills all criteria for a Ph.D. dissertation, and I recommend it for defense. After a successful defense, I recommend granting the academic title of “Ph.D.” to Jaka Fadraersada, M.Sc.**

**Comments and questions:**

1. You described the alteration of lipids in metabolic syndrome patients. Is potential alteration of coagulation related to LDL or HDL cholesterol or both?
2. What are the characteristics of healthy donors with respect to lipids and glucose? Are they in physiological level?
3. Why did the authors analyze the relationship between the international normalized ratio (INR) and other parameters and body mass index (BMI) in healthy donors and not, for instance, waist circumference, which might be more suitable for reducing cardiovascular risk?
4. The author claims that 15 patients with FH were enrolled, but they mention that three homozygous and nine heterozygous patients were investigated. Where are the three missing patients?
5. Did you consider or is there a potential approach to evaluate the effects of anticoagulant drugs with respect to marks of endothelial dysfunction? Is there any information in the literature about his issue?

In Hradec Kralove October 14, 2024.

prof. PharmD. Petr Nachtigal, Ph.D.