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TROMBOFILIAS HEREDITÁRIAS E COMPLICAÇÕES NA GESTAÇÃO: HÁ BENEFÍCIOS NA INVESTIGAÇÃO?

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Objetivos: Revisão da literatura sobre a validade da investigação de trombofilias hereditárias (THs) em gestantes com histórico de complicações na gravidez e/ou eventos trombóticos. **Materiais e métodos:** Pesquisa em base de dados da plataforma Pubmed, utilizando as palavras-chave "inherited thrombophilia", "pregnancy", "screening"e "complications". **Resultados:** Foram selecionados nove artigos de revisão e sete estudos de caso. Nove não recomendam testagem de THs em gestantes, quatro recomendam, dois indicam apenas se há risco significativo de tromboembolismo venoso (TEV), e um recomenda sob risco de TEV mas não especifica conduta para gestantes. Foi apontada pelo boletim n.°197 "Trombofilias Hereditárias na Gravidez"do Colégio Americano de Obstetras e Ginecologistas (em inglês, ACOG) a falta de evidências consistentes de que há associação significativa entre TH e complicações, como perdas fetais, pré-eclâmpsia, restrição de crescimento fetal e descolamento placentário. Oito artigos relatam assimetria regional na prevalência das THs e das complicações gestacionais. **Discussão:** As THs são mutações genéticas que geram um estado de hipercoagulabilidade, seja pela redução da clivagem do fator Va, pelo aumento dos níveis de protrombina, por lesão endotelial na homocisteinemia etc. Essa condição pode ser mais preocupante na gravidez, fisiologicamente caracterizada por um período protrombótico. Assim, a TH é vista como causa de adversidades gestacionais e é tema de interesse científico e também de gestantes com histórico de complicações. Nos artigos de revisão selecionados, os estudos citados se contradizem acerca da prevalência e das complicações das THs em gestantes. Nos estudos de caso, também há contradições. Ademais, os estudos sobre as THs serem fator de risco para as complicações não sustentam uma relação causal capaz de justificar a testagem. Por último, como evidenciado pelo boletim do ACOG, inconsistências em meta-análises e estudos de caso invalidam a profilaxia antitrombótica voltada à redução da incidência de complicações placentárias em pacientes com TH. Porém, há evidência de relação significativa entre THs e TEV, o que fundamenta o grupo de risco elegível para testagem, reconhecido pelo ACOG, definido por histórico de TEV e/ou parente de primeiro grau com TH de alto risco. Isso altera satisfatoriamente o manejo para TEV. Logo, sem benefícios na investigação, visa-se a prevenção quaternária, evitando gastos desnecessários e danos, físicos e emocionais, à paciente. Por fim, percebe-se que dada a natureza multifatorial das complicações gestacionais, bem como o padrão de prevalência das THs, há variações genéticas e comportamentais em diferentes grupos regionais desconsideradas pela prática empírica de testagem e profilaxia. **Conclusão:** Assim, é notória a falta de consenso científico quanto à validade da testagem das THs em gestantes. Portanto, é desnecessária a investigação rotineira de TH em gestantes com história de complicações, exceto se relacionada aos grupos de risco de TEV. Finalmente, enfatiza-se a importância da testagem voltada aos estudos clínicos, sendo estes preferencialmente divididos em grupos regionais, de forma que a relação de causalidade aqui discutida seja adequadamente categorizada.

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TROXERUTIN AS A POTENTIAL THROMBIN INHIBITING DRUG

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Goals: The aim of this work was evaluate using *in silico* methods the troxerutin potential to thrombin inhibition. **Material e metods:** Compounds obtained from medicinal plants with anticoagulant and cardioprotective effects were selected using PubMed, ScienceDirect, and SciELO. The Molispiration server was used for oral bioavailability analysis, and Pred-HERG and Pro Tox-II were used to predict cardiac and systemic toxicities. Analyses of biological activities were performed in PASS online and those of molecular targets in Swiss Target Prediction. Finally, pharmacophoric analysis and molecular docking were performed. **Results:** Among the molecules analyzed for anticoagulant and cardioprotective activities, classified as without pharmacodynamics and with favorable pharmacokinetic profiles, troxerutin, a natural flavanoid derivative, found in the Brazilian cerrado was the most promising and had the highest scores on the servers employed. By predicting the biological activity of this molecule, the effects that corroborated the hypothesis that troxerutin has a anticoagulant activity, such as hemostatic effect, vasoprotection, free radical scavenging, antioxidant, antithrombotic, vasodilator, platelet adhesion inhibitor, therapy for peripheral vascular disease and other descriptions that support the applicability of this species was confirmed. The aglyconated part of troxerutin is absorbable and thus does not present any cardiotoxicity. Evaluation of troxerutin on Pro-Tox II, revealed its toxicity at level 5, with 6 being the lowest. The analysis further revealed inactive hepatotoxicity, cytotoxicity, mutagenicity, carcinogenotoxicity and other toxicities with a propensity of 61% to 97%. Troxerutin fitted with required features of the pharmacophore model of thrombin inhibitors, and a greater part of the molecules was aligned. The three features shared between troxerutin and the thrombin inhibitors with the lowest IC_{50} values indicate that troxerutin may present this inhibitor activity, which was corroborated by molecular docking analysis. **Discussion:** This study showed that thrombin can be considered a potential target to the natural chemical marker troxerutin, which could explain its anticoagulant effects. Furthermore, there is relevant evidence about the anticoagulant effects of the troxerutin, such as

anti-thrombotic, anti-fibrinolytic and rheological activities. To explore the key ligand-enzyme intermolecular interactions between troxerutin and human thrombin, molecular docking simulations were performed using a crystal structure of thrombin. Then, molecular docking was carried out to illustrate the binding mode of the selected flavonoid and the target. The troxerutin could be docked in the catalytic site of human thrombin, indicating that this compound could serve as competitive inhibitor of thrombin, explaining its anticoagulant effects. Thus, this study proposed a potential mechanism that would explain the effects of these species and others that present troxerutin in its composition, besides future assays employing this chemical marker could be corroborated by the data raised in this work. **Conclusion:** The *in silico* approach demonstrated that troxerutin is a promising thrombin inhibitor. *In vitro* and *in vivo* trials using thrombin have shown that it can be a starting point for the development of new therapeutic options with thrombin inhibitors.

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LEUCEMIA LINFÓIDE CRÔNICA E OUTRAS DOENÇAS LINFOPROLIFERATIVAS CRÔNICAS

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COMPARISON OF CLINICAL AND LABORATORY FEATURES, DRUG AVAILABILITY, AND OUTCOMES OF CLL PATIENTS TREATED IN PUBLIC OR IN PRIVATE HOSPITALS IN BRAZIL: A RETROSPECTIVE ANALYSIS OF THE BRAZILIAN REGISTRY OF CLL

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Introduction: Chronic lymphocytic leukemia(CLL) has a highly variable clinical course. It is important to understand the aspects that affect the outcomes of CLL in a real-world setting. Data from the Brazilian Registry of CLL was analyzed to compare clinical and treatment-related characteristics in patients with CLL treated in public or in private institutions in Brazil. **Objective:** To describe the outcomes of a series of CLL patients followed in public or in private hospitals in Brazil. **Methods:** Inclusion criteria for enrollment followed the IWCLL guidelines. We included all patients with minimum available data for analysis of patient and disease characteristics and survival. **Results/Discussion:** From January 2004 to July 2020, 3031 patients from 37 centers met eligibility criteria for this analysis: 2427 (80%) were followed at public hospitals and 604(20%) at private hospitals. The majority were male (57%), with median age of 66 years(range:23-106). Binet stage was A in 1677 (58%) patients, B in 652 (23%), C in 540 (19%). FISH for del(17p) was performed in only 483 patients (16%), while FISH for the most common aberrations [del(13q),+12,del(11q),del(17p)] was performed in only 447 patients(15%). IGVH mutational status was performed in 213 patients (7%), and karyotype in 154 patients (5%). Comparing public and private hospitals, we observed that patients in public hospital are slightly older (median age 66 vs 63 years for private hospitals, $p < 0.0001$), had more advanced diseases at diagnosis (frequency of Binet B or C was 44% in public vs 33% in private hospital, $p < 0.0001$), and there were more patients with elevated creatinine levels(18% vs 10%, $p = 0.03$). All prognostic markers were more available in private than in public hospitals: FISH for del17p(42% of cases vs 10%, respectively, $p < 0.0001$), IGVH mutational status(13% vs 6%, respectively, $p < 0.0001$) and karyotype (16% vs 3%, respectively, $p < 0.0001$). The frequency of del(17p) was similar between public and private hospitals (10% vs 11%, p = NS), while the frequency of unmutated IGHV status was more common in private hospitals, although not statistically different (60% vs 48%, $p = 0.09$). Analyzing 2175 diagnosed after 2008,1019 patients (47%) were treated after a median time of 4 months (range:0-129) after diagnosis. First line treatment was predominantly based chlorambucil (45%) or fludarabine (40%). Anti-CD20 monoclonal antibody was used in only 39% of cases: (rituximab in 35%, obinutuzumab in 4%). Novel agents were used in first line in only 2% of patients. Most patients (86%) with del(17p) detected by FISH were treated with chemoimmunotherapy. When comparing treatments between public or private hospitals we observed striking differences: in public hospitals there were significantly less patients receiving fludarabine-base regimens(34% vs 53%, $p < 0.0001$), and anti-CD20 monoclonal antibodies (27% vs 78%, $p < 0.0001$). Overall survival at 6 years was significantly worse in public than in private hospitals (71% vs 91%, respectively, $p < 0.0001$). Survival in patients from public hospitals remained significantly worse than in private hospitals (hazard ratio 3.9, 95% confidence interval 1.8–8.5), after correcting for age, Binet staging and renal function. **Conclusion:** Our data indicate that there are striking differences between patients treated in public or