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PENELUSURAN POTENSI FASXIATOR SEBAGAI ANTIKOAGULAN ALTERNATIF YANG MENCEGAH TROMBOSIS MELALUI INHIBISI SISTEM AKTIVASI KONTAK

Terobosan Penggunaan Racun Ular dalam Mengencerkan Darah yang Terkoagulasi secara Patologis

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ABSTRAK

Pendahuluan: Trombosis, ketidakseimbangan interaksi dari komponen-komponen darah, berkontribusi besar terhadap kematian yang terjadi di seluruh dunia. Oleh karena itu, diperlukan pengobatan yang dapat membalikkan kondisi pembekuan darah maupun hiperkoagulabilitas. Namun, pengobatan yang digunakan dalam mengobati penyakit yang didasarkan oleh mekanisme trombosis memberikan efek samping yang dapat dilihat dalam jangka pendek maupun jangka panjang, terutama peningkatan risiko pendarahan. Maka dari itu, diperlukan suatu alternatif dalam mengatasi masalah trombosis tanpa menimbulkan efek samping signifikan yang dapat membahayakan nyawa pengguna obat antikoagulan. Solusi dari masalah tersebut tidak lain telah disediakan oleh alam, yakni protease inhibitor yang didapatkan melalui racun ular Bungarus fasciatus, Fasxiator
Pembahasan: Fasxiator dapat mengencerkan darah melalui inhibisi mekanisme Contact Activation System (CAS), secara spesifik menghambat factor XIa. Keuntungan dari inhibisi penggumpalan darah melalui metode CAS adalah tidak terpengaruhnya hemostasis normal sehingga meminimalisasikan permasalahan pendarahan yang lazim terjadi pada penggunaan obat antikoagulan lain. Penelitian pada hewan percobaan tikus menunjukkan selektivitas yang tinggi terhadap faktor XIa, efektivitas, dan profil keamanan yang tinggi dari Fasxiator memungkinkan penggunaan Fasxiator sebagai antikoagulan di masa depan.**Simpulan:** Jelaskan simpulan yang dapat diambil dari isi artikel yang dibuat

Kata Kunci: Antikoagulan, Fasxiator, Hemostasis, Sistem Aktivasi Kontak, Trombosis

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DISSECTING FASXIATOR POTENTIAL AS ALTERNATIVE ANTICOAGULANT BY PREVENTING THROMBOSIS THROUGH INHIBITION OF CONTACT ACTIVATION SYSTEM

Breakthrough of Snake venom usage to thin pathologically coagulated blood

ABSTRACT

Background: *Thrombosis, an imbalanced interaction between blood components, contributes greatly to deaths that occur worldwide. Therefore, treatment that can reverse the condition of blood clotting and hypercoagulability is essential. However, the drugs used to treat thrombosis-based diseases have side effects that can be seen in short and long term, particularly an increased risk of bleeding. Therefore, an alternative treatment is needed to overcome the problem of thrombosis without causing significant side effects that can endanger the lives of anticoagulant drug users. The solution to this problem is none other than nature provided, a protease inhibitor obtained through the venom of the Bungarus fasciatus snake, Fasxiator.*

Discussion: *Fasxiator can dilute blood through the inhibition of Contact Activation System (CAS) mechanism, specifically inhibiting factor XIa. The advantage of blood clotting inhibition through the CAS method is that it does not affect normal hemostasis, thereby minimizing the bleeding problems that are common with other anticoagulant drugs. Animal studies in rats demonstrated properties of high target selectivity for factor XIa, effectiveness, and high safety profile of Fasxiator, enabling the application of Fasxiator as an anticoagulant in the future.*

Conclusion*: Therefore, based on the discussion that has been explained above, Fasxiator has the potential to be used as an anticoagulant on humans in the future due to its high selectivity, effectivity, and safety in previous animal studies.*

Keywords: *Anticoagulant, Contact Activation System, Fasxiator, Hemostasis, Thrombosis*

1. PENDAHULUAN

Human's body has been created to perfectly adapt toward current environment. When there is disruption at skin epithelia barrier, numerous cascades will be executed to patch the hole. Hemostasis is essential to prevent excessive blood loss, thus ensuring adequate organ perfusion.[1] However, dysregulation of this mechanism may lead to thrombosis, which was estimated in 2010 responsible for 1 in 4 death globally.1,2 This pathology encompasses several diseases, including ischemic heart disease, myocardial infarction, ischemic stroke, atrial fibrillation, and venous thromboembolism.[2]

In order to reverse the hypercoagulability state, additional and appropriate anticoagulant is essential to maintain fluidity of blood. However, continued usage leads to high bleeding risk as the current anticoagulant medication disturb the physiological process of normal coagulation, along with other side effects that appear in short and long amount of time application, including osteoporosis, heparin-induced thrombocytopenia, hypersensitivity, interaction with other drug or food, or even damaging kidney organ.1,3 Therefore, alternative anticoagulant targeting other blood clotting mechanism is required to avoid hemostatic disruption and outwit the adverse effect matters. These matters lead to the recommendation of Fasxiator, protein substance collected from Bungarus fasciatus snake's venom that can act as the alternative anticoagulant which does not hinder physiological clotting process, also hopefully able to solve other problems circulating the usual usage of anticoagulant through new approach.

2. PEMBAHASAN

Coagulation process is a harmonic orchestration between blood components in molecular and tissue scales through intrinsic, extrinsic, and common pathways. Vascular injury or hypoxia will commence extrinsic pathway through circulating tissue factor, whereas intrinsic pathway will be commenced through contact between factor XI, XII, prekallikrein, and high molecular weight kininogen (HK) with kaolin or other molecules such as extracellular DNA, RNA, and inorganic polyphosphates, depending on site activation. Both intrinsic and extrinsic will lead to the activation of factor Xa that initiates common coagulation pathway.[1]

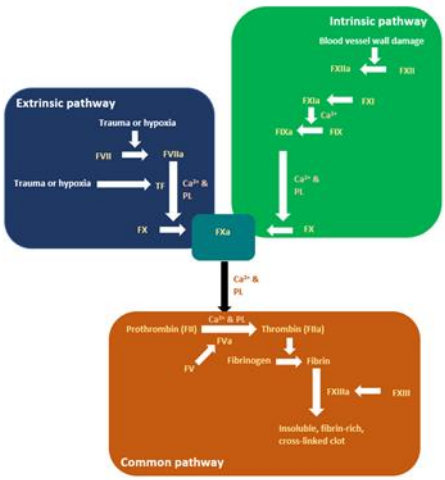

Figure 1. Coagulation pathways.[1]

Intrinsic pathway, or infamously known as Contact Activation System (CAS) has become the center of study spotlight recently. Despite of the hereditary deficiency of intrinsic pathway components, those who are inflicted have no bleeding problem issues.1 From those findings, researchers speculated less significant role of CAS toward hemostasis at peripheral sites, merely amplifying factor Xa thus multiplying thrombin formation.[1,4] Another study discovered that lack of CAS components, especially prekallikrein and factor XII, significantly protect retinal and brain vasculature, decreasing hemorrhage chance at those areas.[4]

Because of the lack of importance in physiologic hemostasis consisting of vasoconstriction and local platelet aggregation, CAS factors have been targeted as potential therapeutic target.[4] There are many candidates emerging based on this discovery, mainly inspired by natural physiologic process of animals' daily activities and arsenal weapons. One of those candidates is Fasxiator, protease inhibitor harvested from Bungarus fasciatus snake's venom. Even though the overall population of that snake is stable currently with several reported local endangerment, should this breakthrough utilized widely, strict regulation must be maintained to keep the ecology and biodiversity stable.[5] Fasxiator selectively inhibits factor XIa, leaving other components intact and undisturbed. This property emphasizes apparent margin of selectivity up to 6000x with the highest concentration of Fasxiator tested 120 µM. At one study, the usage of Fasxiator resulted in double clotting time during Activated Partial Thromboplastin Time (APTT) assay by using only small amount of dose (3µM) while did not influence distinctly Prothrombin Time (PT) using concentration as high as 100µM.1 The experiment involving mice with FeCl3-induced occlusive thrombosis produced protective result with Fasxiator dose 0.3 mg/animal.[1,6]

However, the utilization of original Fasxiator inhibited chymotrypsin, proteolytic enzyme required in digestive system with value of IC50 1µM. Therefore, series of mutated Fasxiator have been created to further improve potency and selectivity of Fasxiator. In one study, FasxiatorN17R,$_{L19E}$ had shown great promise in selectivity index of more than 100 fold over chymotrypsin, the obstacle previously encountered at original Fasxiator. The effectiveness and potency of this mutant Fasxiator remained the same, if not increased. Not to mention, Fasxiator $_{N17R,L19E}$ was 10 times more potent in human plasma compared to experimental rat.[1] The safety profile had also been proved in experiment using rodent tail vein bleeding model. Compared to the usage of unfractionated heparin, Fasxiator generated lower bleeding risk concomitant with the rise of dose. The study showed that the bleeding time caused by mutant Fasxiator (FXI001) was only 1.7x above control subject (using saline), whereas unfractionated

heparin bleeding time raised more than 7x above control subject.[7]

3. KESIMPULAN

As disharmony of hemostasis components interaction continues to dominate global dead cause, the solution toward this everlasting problem is continuously sought. The usual medication given to restore the balance induces short-term and long-term side effects, mainly bleeding. Therefore, another alternative is required to reduce complications. Nature gift might have provided the answer through exceptional course.

The protease inhibitor obtained through Bungarus fasciatus snake's venom, Fasxiator, shows great promise to reverse hypercoagulability state via inhibition of Contact Activation System (CAS), specifically inhibiting factor XIa. This method allows Fasxiator anticoagulant to reduce blood clotting without interfering with hemostasis, solving bleeding problem encountered by other anticoagulant mechanism. The margin of selectivity, effectivity, and safety of Fasxiator in experimental animals further highlight the potential of Fasxiator as alternative anticoagulant in the future.

However, to ensure the efficacy and safety of Fasxiator in human, further studies are required, especially concerning any short- or long-term effects developed after Fasxiator usage. More investigations regarding the best model of Fasxiator mutants are also crucial to increase the efficacy and safety of Fasxiator application in human as well, ensuring remarkable result to prevent future pathological thrombosis-based diseases.

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