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Popular naturally occurring antioxidants as potential anticoagulant drugs

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ABSTRACT

Blood coagulation is a physiological process whose main task is prevention of blood loss from injured vessels. This process consists of a series of zymogens proteolytic activation leading to the generation of the main coagulation enzyme – thrombin. Besides its important role in blood coagulation process, thrombin is involved in many cardiovascular diseases, which are responsible for almost half of fatalities in economically developed countries. The evidence for the increased generation and in vivo activity of thrombin was observed in the plasma of individuals at high risk for clinically significant venous and arterial thromboembolic complications.

Antioxidants activity of plants extracts has been well known for many years and was confirmed by many publications. However, during the last decade many research centers presented results suggesting anticoagulant potential of various plant extracts. Many researchers have also provided evidence that polyphenol compounds are able to inhibit the activity of many enzymes, including serine proteases.

All research described in this review clearly indicate that polyphenols and polyphenol-rich extracts possess not only antioxidative but also anticoagulant properties and may be useful in creation of new therapeutic agents or dietary supplements. Based on described properties polyphenols would be very helpful with both prevention and treatment of thromboembolic complications associated with multiple failures of haemostasis, because the available therapeutic agents do not offer such double-effects (antioxidant and anticoagulant).

Contents

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1. Introduction

It is estimated that almost half of the fatalities in both the economically developed countries and developing countries is directly or indirectly associated with cardiovascular diseases. The incidence of cardiovascular diseases and their complications makes that group of conditions "the greatest epidemic of our times" [1]. Cardiovascular diseases are furthermore causes of multiple patients hospitalization, deterioration of their physical and mental efficiency and often lead to permanent disability, generating very high socio-economic costs [2]. Amongst cardiovascular diseases the key problem is thromboembolic complications which pathogenesis consist of a critical blockage in blood vessels caused by a forming blood clot [3]. Those disorders are the result of irregularities in the functioning of haemostatic system related mainly with invalid mechanisms controlling thrombin formation and activity. Increased thrombin activity results in thrombus generation in the blood vessels, which in turn results in thrombotic events [4].

The researches accomplished in recent years have provided evidence that plant extracts which have strong and well known antioxidant properties have also anticoagulant effects.

Additionally much research shows that polyphenol compounds which are present in plant extracts, are able to inhibit the activity of many enzymes, including serine proteases [5]. Many epidemiological studies have confirmed the antithrombotic effect of polyphenol rich plant extracts [6].

2. Blood coagulation process

Blood coagulation is a physiological process which main task is prevention of blood loss from injured vessels. This process consists of a series of zymogens proteolytic activation leading to the generation of the activated enzyme – thrombin [7]. In the first phase of cell based coagulation process (called initiation phase) the tissue factor (TF) present in cells and exposed in injury site contacts with the circulating blood and forms with the coagulation factor VIIa (FVIIa) on a cell surface FVIIa/TF complex [8]. The Factor VII is the only coagulation factor which in the physiological conditions is found in the blood in an active form (approximately 1% of the total plasma pool), while other proteins involved in the blood coagulation process circulate in blood only as inactive zymogens [9].

The FVIIa/TF complex is responsible for the proteolytic activation of two coagulation factors: FX and FIX. Activated FX forms the complex with its cofactor FVa on the TF-bearing cell prothrombinase complex. The complex is responsible for the conversion of small amounts of prothrombin to thrombin [10–12]. Generation of small amounts of thrombin initiates the second phase of blood coagulation called amplification phase [13]. In this phase blood platelets circulating in blood adhere to components of the extracellular matrix exposed at the injury site. Subsequently blood platelets through PAR (Protease Activated Receptors) are activated by thrombin. Thrombin-activated platelets cause the change in their shape and exposes a negatively charged phosphatidylserine, which is necessary to interact with the γ-carboxyglutamic acid (Gla) residue in plasma coagulation factors and coagulation enzymatic complexes formation [14]. Additional activated platelets forms aggregates, which increases a negatively charged surface necessary for coagulation factors interactions [15].

Besides blood platelets' activation, thrombin generated in the initiation phase activates other plasma coagulation factors (FXI, FVIII, FV), which bind on the activated platelets' surface. After thrombin-induced activation of plasma coagulation factors propagation phase takes place. In that stage platelet-bound FXIa converts FIX to FIXa which with its cofactor FVIIIa forms on blood platelets' surface a tenase complex which generates more active form of FX [16,17]. Under some physiological conditions, approximately 50-fold more factor Xa is formed by the tenase complex than the TF/VIIa complex [8]. Activation of a large amount of FX causes formation of multiple prothrombinase complexes which as a result of the feedback generates a large amount of thrombin. This phenomenon is referred to as "thrombin burst" [18].

In the last phase of blood coagulation (effector phase) generated thrombin causes conversion of plasma-soluble protein - fibrinogen into insoluble fibrin clot [19–22]. Formed fibrin clot is subsequently stabilized by factor XIII activated by thrombin. The factor XIII is a plasma transglutaminase which introduces covalent ε-(γ-glutamyl) lysine cross-links in the fibrin polypeptide chain, increasing the mechanical strength of the fibrin clot and protecting against the fibrinolytic degradation [23–25]. The scheme of coagulation cascade with the targets of available medicines was presented in Fig. 1.

3. Thrombotic coagulation disorders

Thromboembolic diseases are a leading cause of morbidity and mortality worldwide. These pathological conditions are caused when a blood vessel is obstructed by a blood clot (embolus) that has been carried in the bloodstream from the site of its formation. All of these disorders are caused by the malfunction of the haemostatic system and are connected with impaired mechanisms controlling the formation and activity of thrombin. This leads to the formation of clots in blood vessels and consequently to thromboembolic complications. Thromboembolic disease includes both venous thromboembolism (VTE) when a clot is formed in vein and arterial thrombosis when a clot is formed in an artery. VTE is a general term which refers to mainly two conditions: deep vein thrombosis (DVT) and its potentially fatal acute complication: pulmonary embolism (PE). DVT refers to the formation of blood clots in one of the body's large veins (most common in legs). Formed clots can cause partial or absolute blocking vein circulation. PE occurs when the blood clot from a vein breaks loose and travels in the bloodstream - first to the

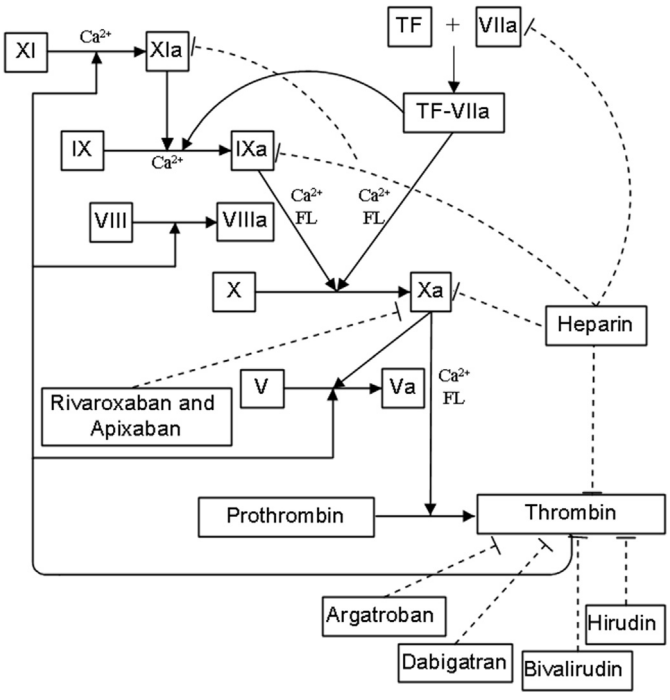

Fig. 1. Scheme of coagulation process with targets of available medicines.