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Review

THE ROLE OF ANTICOAGULANT, THROMBOLYTIC, AND FIBRINOLYTIC ACTIVITIES IN THE PREVENTION OF PERITONEAL ADHESION

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Abstract: Peritoneal adhesion occurs as a result of surgery, peritoneal injury, peritonitis, hypoxia, and ischemia. Surgical trauma causes many pathophysiological processes which include inflammation, oxidation, coagulation, fibrinolysis, cell proliferation, and apoptosis. After intra-abdominal operations, the adhesion tissue may occur on the peritoneal surface due to low fibrinolytic activity. This may result in permanent excessive adhesion tissue bands instead of properly formed fibrin structures. Therefore, anticoagulant, thrombolytic, and fibrinolytic activities have a key role in preventing peritoneal adhesion. Indeed, several studies have been conducted to find out new and effective agents against intra-abdominal adhesion. Thus, revealing the causes, development processes, and investigation techniques are highly important for designing and conducting such scientific studies. In this context, this study aims to summarize the pathophysiological processes of above-mentioned activities and to emphasize their importance in the peritoneal adhesion model as well as to explain the evaluation methods, particularly in terms of the investigation of natural products.

Özet: Peritoneal adezyon cerrahi, peritoneal yaralanma, peritonit, hipoksi ve iskeminin bir sonucu olarak ortaya çıkar. Cerrahi travma, inflamasyon, oksidasyon, pıhtılaşma, fibrinoliz, hücre proliferasyonu ve apoptozu içeren birçok patofizyolojik sürece neden olur. Karın içi operasyonlardan sonra, düşük fibrinolitik aktiviteye bağlı olarak periton yüzeyinde adezyon dokusu oluşabilir. Bu, uygun şekilde oluşturulmuş fibrin yapıları yerine kalıcı aşırı adezyon doku bantları ile sonuçlanabilir. Bu nedenle, antikoagülan, trombolitik ve fibrinolitik aktiviteler peritoneal adezyonu önlemede anahtar role sahiptir. Nitekim karın içi yapışıklığa karşı yeni ve etkili ajanlar bulmak için birçok çalışma yapılmıştır. Bu nedenle nedenlerinin, gelişim süreçlerinin ve inceleme tekniklerinin ortaya konulması, bu tür bilimsel çalışmaların tasarlanması ve yürütülmesi açısından oldukça önemlidir. Bu bağlamda bu çalışma, yukarıda bahsedilen aktivitelerin patofizyolojik süreçlerini özetlemeyi, peritoneal adezyon modelindeki önemini vurgulamayı ve özellikle doğal ürünlerin araştırılması açısından değerlendirme yöntemlerini açıklamayı amaçlamaktadır.

Introduction

The adhesion tissue can cause many critical complications in patients undergoing surgery such as intestinal obstructions, chronic abdominal pain, infertility, and re-operations. Recurrent adhesions are more complicated and difficult to prevent than primary adhesions and have a high incidence. Although adhesions are mostly asymptomatic, they may result in morbidity and mortality by causing the patient to undergo re-operation. They also impose a financial burden on the health system. There are many treatment methods reported in the literature affecting various pathways. Cell proliferation, apoptosis, inflammation, oxidation, coagulation, and fibrinolysis take part in the pathophysiology of adhesion (Hu *et al*. 2021). The remedies that affect these processes show preventive and curative effects on adhesions. For the prevention and healing of peritoneal adhesions, traditional medicines can be used (Zhou *et al*. 2016, Wu *et al*. 2020).

Repairing process of the peritoneal adhesion is similar to the wound healing process. Both processes initiate with the injury or damage of an area in the body. They also include the same progression such as inflammatory response, hypoxia, coagulation, cell

migration and proliferation (Süntar *et al*. 2021). From an ethnobotanical point of view, the use of natural remedies for wound healing is very common among people living in rural areas. For instance, *Hypericum perforatum* L. ,*Centella asiatica* (L.) Urban, *Plantago lanceolata* L., *Plantago major* L. subsp. major, *Rubus hirtus* Waldst & Kit., *Sambucus ebulus* L., *Morus alba* L., *Hedera helix* L., *Kalanchoe blossfeldiana* Poelln., *Ononis spinosa* L. subsp. Leiosperma (Boiss.) Sirj., *Kalanchoe blossfeldiana* Poelln., bitter honey and propolis are used in folk medicine as wound healing agents (Süntar *et al.* 2014, Süntar, 2014, 2020, Miser-Salihoğlu *et al*. 2013, Gürbüz *et al*. 2019). These medicinal plants can also be selected as promising agents to investigate their effects on peritoneal adhesion considering their similar activity mechanisms in proper healing. For instance, *Rumex crispus* L. root extract was shown to display preventive effect on post-operative abdominal adhesion model in rats, based on its anti-inflammatory potential (Süntar *et al*. 2021).

Barrier methods, pharmacological agents, and properly operating methods are frequently used in clinical treatments (Lauder *et al*. 2010, Schnüriger *et al*. 2011). Agents targeting angiotensin, hypoxia-inducible factor inhibitors and N acetyl cysteine, hydroxy 3 methyl glutaryl coenzyme A reductase inhibitors, neurokinin 1 receptor antagonists, lubricin as mucine like proteoglycant, chymase inhibitors and sodium cromoglycate, NSAIDs and anti-inflammatory drugs, small molecule inhibitors and hormones (estrogen and ghrelin) can be used for their anti-adhesive properties on various mechanisms in coagulation cascade and inflammatory pathways (Fatehi Hassanabad *et al.* 2021, Flutur *et al.* 2023). The gene expression is a new method that has a preventive effect on adhesion formation (Liu *et al*. 2006). Although not much in number, there are studies on the use of gene therapy including adenovirus vectors that code human tissue plasminogen activator (tPA) gene, hepatocyte growth factor gene and sphingosine kinase 1 gene for adhesion prevention (Liu *et al.* 2006, Guo *et al.* 2007, Nair *et al.* 2013). The pharmacological agents exert anticoagulant, fibrinolytic, anti-inflammatory, antioxidant, and collagen synthesis inhibition activities (Arung *et al*. 2011). Among these activities, the fibrinolytic activity has substantial impact on adhesions. The stable fibrin matrix can transform into adhesion tissue or degradation products. Fibrin structure is converted to degradation products by means of plasmin, which is the major component in fibrinolysis. Thus, the healing process dominates instead of permanent adhesion tissue (Schnüriger *et al*. 2011).

General Information on Peritoneal Adhesion

Adhesion formation is a variant of the normal peritoneal healing process and the permanent connections between intra-abdominal surfaces are called adhesion tissue (Diamond & Decherney 1987). As a result of injury to the peritoneum by traumatic factors such as mechanical, chemical, thermal, infection, or foreign body reaction, adhesion occurs due to the contact of the basement membrane of the mesothelial layer with the surrounding tissues. Adhesion development is observed in 97% of the gynecological and 67-93% of the intra-abdominal surgery cases (Vrijland *et al*. 2003, Menzies & Ellis 1990). Adhesion causes many complications, including bowel obstruction, infertility, and pain, and also can lead to the inhibition of the homogeneous distribution of drugs in the peritoneal cavity (Clercq *et al*. 2016). In fact, adhesions are a defense mechanism of the body against peritoneal damage (Duron *et al*. 2007). These bonds; can vary from a thin band of connective tissue to a thick, fibrous adherent with the dense vascular formation or a direct connection between two organ surfaces. Fibrinous exudate is involved in tissue healing and fibrin-rich fluid causes a local inflammatory response and angiogenesis. In a normal healing progression, fibrin breaks down by the destructive action of plasminogen and returns to normal. If the fibrinolytic activity is not sufficient, adhesion tissue is formed (Hellebrekers & Kooistra 2011, Fometescu *et al*. 2013). Along with fibrinous adhesion, vascular growth and an increase in collagen structure are also observed (Hellebrekers *et al*. 2000). Hence, the destruction of the fibrin structure is important for healing (Hellebrekers & Kooistra 2011). Plasminogen is converted to its active form, plasmin, by urokinase-type plasminogen activator (uPA) and tPA it is inhibited by plasminogen activator inhibitor-1 (PAI-1). Plasmin plays an important role in fibrinolysis and breaks down the fibrin-structured adhesion tissue (Vipond *et al*. 1990). PAI-1 is generated and released by macrophages, platelets, endothelial cells, mesothelial cells, and fibroblast cells. The level of PAI-1 is affected by macrophages, thrombin, endotoxin, transforming growth factor-beta (TGF-β), interleukin-1, and tumour necrosis factor (TNF) (Colucci *et al*. 1985, Nachman *et al*. 1986, van Hinsbergh *et al*. 1988, van Hinsbergh *et al*. 1990, Sitter *et al*. 1995, Cheong *et al*. 2001). It was reported that with adhesion formation in patients, the PAI-1 level increased but the tPA level decreased in the peritoneal tissue which resulted in a decrease in fibrinolytic activity (Fometescu *et al*. 2013).

Inflammation and the Coagulation Cascade

In the case of injury, tissue damage initiates the coagulation cascade. In order to create a cellular response in intra-abdominal damage, inflammatory and procoagulant agents in the local vein, mesothelial tissue, and peritoneal fluid migrate to the damage region. In the first part, tissue damage platelets are a crucial compound of the inflammatory exudate. Healing of the peritoneum begins within 2-3 days. After the injury, prostaglandin E2 and histamine secretion increases, and thus vascular permeability increases. As a result of the increase in vascular permeability, serosanguineous, protein-rich exudate accumulates in the peritoneal cavity and coagulates within three hours. The fibrinous structure formed as a result of coagulation adheres to the damaged area of the peritoneum and is infiltrated by inflammatory cells. If there will be a normal recovery, the fibrinous

structure formed is dissolved and the resulting degradation products are absorbed. The absorption mechanism requires sufficient plasminogen activator activity in the mesothelial and submesothelial vascular structures. This fibrinolytic activity normally begins on the third day following the peritoneal injury and reaches its peak on the eighth day. Normal healing occurs when the fibrin is completely broken down (Raftery 1979).

Megakaryocyte is the bone marrow cell responsible for platelet production and platelets have granules that allow bioactive proteins to be released into damaged areas. Platelet-derived growth factor (PDGF) and TGF-β are released by the platelets and epinephrine and serotonin are secreted by the dense bodies in the platelets, thus supporting the production of prostaglandins and leukotrienes (Rendu & Brohard-Bohn 2001). Whereas chemokines canalize the migration of cells to the area of the injury, platelets contribute to the initial fibrin clot, and the coagulation phase starts.

Fibrin deposition connects adjacent surfaces and contributes to adhesion formation. Peritoneal adhesion originates from a fibroproliferative inflammatory reaction sequence. Stimulation of proliferation, differentiation of fibroblasts, and secretion of plasminogen activators are regulated by macrophages. Macrophages have a key role in healing tissue damage. Ar'Rajab *et al.* (1995) demonstrated that the induction of peritoneal macrophages significantly reduced the degree of peritoneal adhesion. The fibrin bond between adjacent surfaces in the peritoneal layer can be broken down by the activity of fibrinolytic agents. However, when fibrin bonds multiply with cells, they become stronger (DiZerega & Rodgers 1992). In summary, damage to the peritoneal tissue, with the onset of bleeding, leads to the formation of fibrin that adheres to adjacent surfaces (Harris *et al.* 1995). If the fibrin structure is not broken down, it grows into a fibrin network and adhesion formation occurs within a week (Eskeland 1966).

Both in preclinical and clinical studies, inflammatory cytokines (tumour necrosis factor-alpha (TNF)-α, interleukin (IL)-1, IL-6) increased in the peritoneal tissue repair process. On the other hand, the level of TGF-β, IL-1, IL-6, and TNF-α decreased during the fibrinolysis process (Holmdahl & Ivarsson 1999). Briefly, the levels of cytokines can change throughout coagulation, fibrinolysis, and healing. The progression of adhesion is linked to the response of acute inflammation (Fig. 1) (Hu *et al.* 2021). Ambler *et al.* (2012) demonstrated that TNF-α increased by 58% in adhesive fibroblasts compared to normal fibroblasts. IL-6 produces a systemic inflammatory response. TNF-α and IL-6 are thought to have a role in regulating the formation of a fibrin coagulation cascade (Ambler *et al.* 2012). Uyama *et al.* (2019) argued that peritoneal adhesion progress is reduced by using IL-6 receptor antibody. Other inflammatory agents (IL-17 and IFN-γ) have also succeeded to inhibit the development of peritoneal adhesion (Wang *et al.* 2014, Ohashi *et al.* 2014, Kosaka *et al.* 2008). Briefly, the extent of the damaged area affects the severity of the inflammatory response, while the degree of the inflammatory response affects adhesion formation.

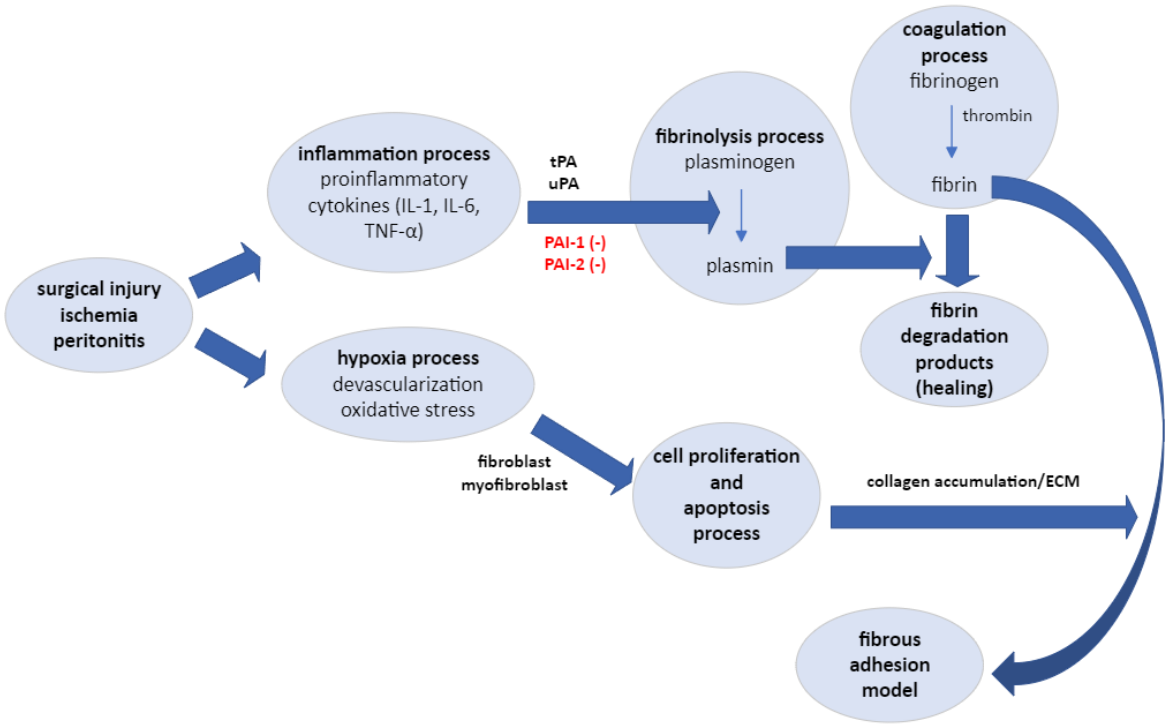

Fig. 1. The process of adhesion and healing.

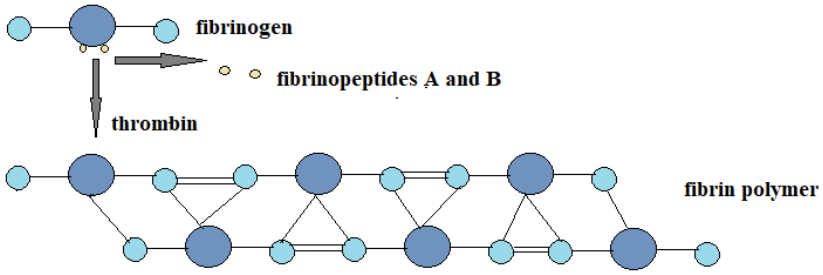

Fig. 2. The formation of fibrin.

With the onset of a trauma within the intra-abdominal surface, tPA levels decrease, and plasminogen activator inhibitor-1 (PAI-1) concentrations increase. As a result, the fragmentation of the fibrinous structure accumulated in the peritoneum decrease (Whawell & Thompson 1995). The main cause of permanent fibrous adhesions is the persistence of the fibrin deposition. TNF, IL-6, and IL-1 inflammatory cytokines increase and regulate PAI-1 levels released by endothelial cells. These ideas show that cytokines interact with cells involved in the production of tPA and PAI-1 and partially affect PAI-1 production, thus causing adhesion formation and development. IL-6 produces an acute phase inflammatory response and stimulates cascades of inflammation, fever, and coagulation. It has adhesion-related activity in processes such as angiogenesis, fibrinolysis, and alteration of the extracellular matrix (ECM) (Holmdahl & Ivarsson 1999).

The presence of mesothelial cells at the wound site causes wound healing or fibrosis and the formation of ECM. Various growth factors, including TGF-β, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), Insulin-like growth factor (IGF), and fibroblast growth factor (FGF) and cytokines are responsible for the duration of ECM deposition. From 1 week to 1 month, the ECM is strengthened and shaped. Thus, the permanent protein collagen replaces the ECM molecules, and the revascularization process continues (Genevieve & Weigel 2006).

The mechanism of fibrin formation and degradation

In case of injury, the hemostatic system provides the balance between fibrin formation (coagulation) and fibrin dissolution (fibrinolysis) processes in order to repair the injured area, prevent blood loss, and ensure circulation (Riddel *et al*. 2007). The hemostatic system is a process in which blood coagulation begins immediately and is rapidly completed with many cascades (Orkin *et al*. 2014). Coagulation occurs for the purpose of defense in the body and then platelets form a hemostatic plug by attaching to the macromolecules of the subendothelial tissue in that area. Platelet aggregation and fibrin clot are degraded in the following period, during the normal healing process (Riddel *et al*. 2007). Thrombin transforms fibrinogen into fibrin (Fig. 2), but plasmin is the main enzyme that can break down both fibrinogen and fibrin (Monroe *et al*. 2002). Disruption of this process can cause clotting or bleeding. Besides high fibrinolytic activity may turn into a risk of bleeding or coagulation (Rasche 2001).

Heparin, a well known anticoagulant agent, was found to be successful in the prevention or reduction of peritoneal adhesion in *in vivo* models (Kement *et al*. 2011, Sharifi *et al*. 2007). In the rabbit uterine adhesion model, thromboxane synthetase inhibitor and thromboxane A2 receptor blocker were found to be effective in reducing the severity of the adhesion (Legrand *et al*. 1995).

Intrinsic and extrinsic pathways are components of the coagulation cascade (Fig. 3) (Riddel *et al*. 2007). The coagulation process is initiated by the tissue factor (thromboplastin) in the subendothelial cell membrane in the external pathway and by blood factors in the internal pathway. When coagulation is initiated, Factor X activate, and as a consequence the fibrin structure occurs in the common pathway (Luchtman-Jones & Broze 1995). Factor Xa, the active form of Factor X, transforms prothrombin to thrombin in the common pathway (Harmening 2002). Thrombin plays a key role in fibrin formation by activating fibrinogen and is also responsible for the formation of cross-linked fibrin structures by converting FXIII to its active form FXIIIa (Boron & Boulpaep 2005).

Conditions such as low fibrinolytic activity, hypoxia, and large damaged area lead to an imbalance of procoagulation and fibrinolytic processes, which cause fibrin deposition. When the peritoneum is damaged in a state of hypoxia, the coagulation cascade changes and activates the formation of fibrous matrix and fibrin structures. Under normal conditions, fibrin structures are transformed into fibrin degradation products by plasmin. Plasminogen activator is classified into tPA and urokinase-type (uPA) (Koninckx *et al*. 2016). Holmdahl *et al*. (1996) claimed that tPA is responsible for the regulation of fibrinolytic activity in the peritoneum, as well as plasminogen activating effect at a rate of 95%. tPA is controlled and inhibited by PAI-1. In cases where the intra-abdominal wound is large, the balance between tPA and PAI-1 is disturbed, and fibrin exudate may increase and cause a solid and permanent fibrotic structure (Koninckx *et al*. 2016). The rate of fibrinolysis decreases, and then fibroblasts attach to permanent fibrous structures, causing ECM production.

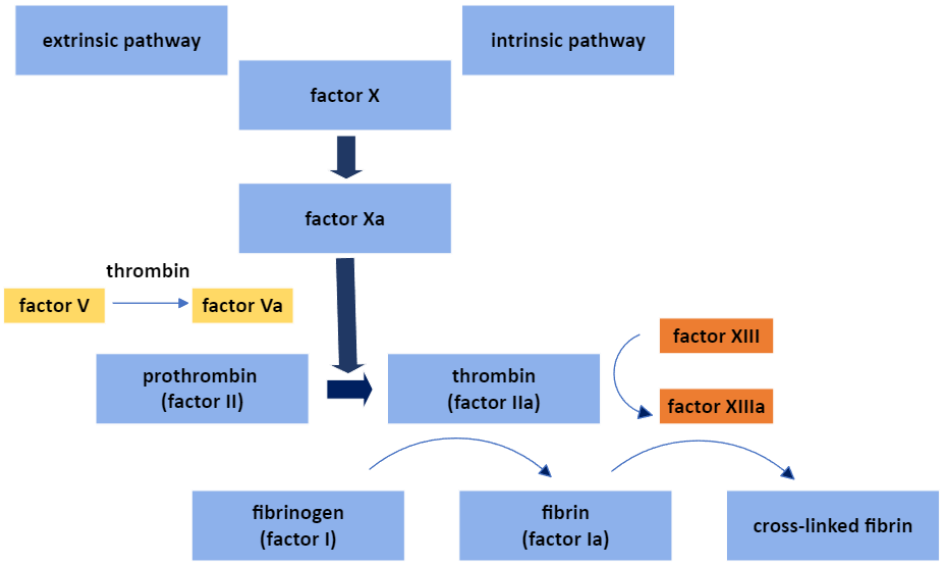

Fig. 3. The common pathway of coagulation.

As a result, the ground for the formation of peritoneal adhesion is prepared, tPA activity may decrease with the inflammatory response, followed by a reduction in fibrinolytic activation with remission in the tPA/PAI ratio, resulting in adhesion formation.

Fibrin is formed during tissue repair after abdominal damage and is activated by the fibrinolytic system. During the healing period, fibrin dissolves over time, but if it is not resolved, it turns into fibroblasts and abdominal adhesion occurs. Plasminogen and plasmin, plasminogen activators including tPA, uPA, fibrinolysis inhibitors including PAI-1, α2-antiplasmin (α2-AP), and enzymatic reactions take place in the fibrinolytic system (Tang *et al*. 2020).

The precursor molecule plasminogen is converted to active form plasmin by tPA and uPA. PAI-1 activity prevents this conversion. tPA is generally released by vascular endothelial cells, mesothelial cells, and macrophages and has a high affinity for fibrin (Moris *et al*. 2017). The fibrin-tPA complex activates plasminogen. The main role of plasmin is to partition to fibrin. Both PAI-1 and PAI-2 inhibit tPA and uPA at different rates. In this process, interaction occurs between the inhibitors and the activators. The fibrinolytic process is responsible for the adhesion to be formed after the operation (Cheong *et al*. 2001).

In damaged peritoneal tissue, the activity of peritoneal plasminogen activators is severely reduced (Porter *et al*. 1969, Hau *et al*. 1979, Raftery 1981, Thompson *et al*. 1989, Holmdahl *et al*. 1997), and the concentration of PAI is partly increased (Vipond *et al*. 1994, Holmdahl *et al*. 1997). When patients, who underwent laparotomy, with mild or moderate adhesions were compared in adhesion tissue and peritoneal tissue biopsy, it was found that PAI-1 was high in severe adhesions, and tPA activity was decreased in the peritoneal tissue next to the adhesion sites (Ivarsson *et al*. 1998).

Assessment of Fibrinolytic, Anticoagulant, and Thrombolytic Activities

There are many methods used to measure the formation and degredation of fibrin. Prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (TT) are related to coagulation, and the fibrin plate method and euglobulin time are associated with the fibrinolytic cascades. There are also numerous assessment methods for inflammation, oxidation, and coagulation processes.

Euglobulin time and fibrin plate are methods for measuring fibrinolytic activity. In a study by Urano *et al*. (1990), the relation of euglobulin clot lysis time (ECLT) with tPA and PAI was investigated using the plasma of healthy volunteers and both tPA and PAI-1 have been found to be associated with ECLT. ECLT shows whether fibrinolytic activity exists and the amount of free PAI-1. In the ECLT measurement, blood samples are taken and procedures are performed in the test tube to obtain the euglobulin fraction. With the addition of thrombin, clot formation is initiated. It is based on measuring the euglobulin clot lysis time and measurement is made according to the onset of coagulation. If the amount of fibrinogen is low, ECLT is ineffective for measuring the fibrinolytic activity (Ilich *et al*. 2017). This method was first designed by Kowarzyk & Buluk (1950).

The fibrin plate method is also used to determine the fibrinolytic activity (Astrup & Mullertz 1952). Sample and plasmin reference is applied to Petri dishes covered with agarose and fibrin layers. This method is based on the comparison of the melting areas they form after the incubation period.

In the method of labeling the fibrinogen with a fluorescent agent, fluorescein isothiocyanate (FITC) is added to a 2% fibrinogen solution in alkaline media and is allowed to incubate at 4°C. The fibrinogen-FITC complex is separated by G100 Sephadex column chromatography. Calcium chloride is added to the plasma

sample and fibrinogen-FITC complex solution to prepare a labeled clot and then is incubated for 80 minutes at 37°C. Centrifugation is done for clot formation, then plasma is added to the medium for fibrinolysis assay. Labeled clot fluorescence is measured by a spectrofluorometer and recorded as a negative control. Different concentrations of the plant extracts and positive control are added to the plasma separately. The measurement of these samples is made with a spectrofluorometer. The fluorescence intensity is measured by comparing the fibrinolytic effect with the positive control.

PT, APTT, and TT tests are used in the clinic to assessment of anticoagulation activity. Partial thromboplastin time (PTT) analysis is performed to measure the intrinsic pathway of the coagulation cascade (Hoffman *et al*. 2005, Liu *et al*. 2018). The PT test evaluates the external pathway of the coagulation cascade (Liu *et al*. 2018). The capacity to convert fibrinogen to fibrin is assessed by the TT measurement (Yang *et al*. 2022). Human or animal blood samples are needed to make these measurements.

Qi *et al*. (2012) reported that the elongation of the APTT pointed out the inhibition of common and/or intrinsic pathways of coagulation. The conversion of fibrinogen to fibrin by thrombin is associated with TT. Prolongation of TT is thought to be related with the breakdown in the fibrin network or thrombin inhibition. When tissue damage occurs, the extrinsic pathway is activated as an immune response, and a fibrin clot is formed. The intrinsic pathway is activated independently of tissue damage, resulting in a thrombus or clot formation.

Optical aggregation is a technique that indicates turbidimetrically platelet aggregation. Firstly, the platelet-poor plasma (PPP) is prepared. PPP is mixed with diverse aggregate agents including collagen, arachidonic acid, thrombin, adenosine difosfat, and then the mixture is incubated. Aggregation is measured with a computer-connected Lumi-aggregometer, and the change in light transmission is determined as a percentage by comparing the value of the sample without aggregate (Seo *et al*. 2012, Jung *et al*. 2002).

In the clot lysis testing, blood samples from normal human plasma and rabbits are transferred into sterile Eppendorff tubes. Then the sampels are incubated at 37°C for 45 minutes for clot formation. In case of clot formation, the clot is completely separated from the serum and for the calculation of clot weight the tubes having clots are weighed again to calculate clot weight. The sample solution is added to the tubes having clots. The control tube is distilled water and the entire tube is incubated at 37°C for 90 minutes. After removal of the fluid released with clot dissolution, the tubes are reweighed to find the weight difference. The percent clot dissolution is the difference in weighing before and after clot lysis (Prasad *et al*. 2006). Alamgeer *et al*. (2018) demonstrated that aqueous-methanolic extract of *Berberis orthobotrys* Bien. ex Aitch. has thrombolytic activity and concluded that it might be a candidate for use in cardiovascular treatment. Ethanolic extract of *Clausena heptaphylla* (Roxb.) Wight & Arn. possess clot lysis ability so its thrombolytic activity is remarkable compared to streptokinase (Fakruddin *et al*. 2012).

Most of the studies performed so far on plant extracts and secondary metabolites used the methods described above. These *in vitro* methods can investigate the presence of the mentioned activities in medicinal plants. When *in vitro* study models are examined, differences are observed in the parts of the plant used, extract type, dose, route of administration, and activity. Shanti *et al*. (2021) demonstrated that fucoidan isolated from *Turbinaria decurrens* Bory de Saint-Vincent possess an anticoagulant effect, covering with silver nanoparticles (fucoidan-coated anionic AgNPs) can be a possible drug candidate, and that it is crucial to guide drug research. Its anticoagulant activity was investigated by using an activated partial thromboplastin time (aPTT) assay. The aqueous extract of *Bulnesia sarmienti* Lorentz ex Griseb. highly inhibited thrombin, ADP-induced, or collagen platelet activation through an aggregometer, showing that plant based products can be investigated for their antiplatelet and antithrombotic potential (Kamruzzaman *et al.* 2010).

Fibrinolytic, Anticoagulant, and Thrombolytic Activities of Natural Products

Fibrinolytic enzymes such as streptokinase, urokinase, staphylokinase, and bafibrinase are derived from natural origins including microorganisms, mushrooms, plants, parasites, snake venoms, and earthworms (Altaf *et al*. 2021). Streptokinase is a fibrinolytic enzyme of microbial origin used as a thrombolytic agent. The enzyme is produced by β-hemolytic streptococci and it activates the plasminogen and dissolves the thrombus (Kotb 2012, Banerjee *et al*. 2004). Nattokinase is obtained from a traditional Japanese food called Natto and is formed as a fermentation product of *Glycine max* (L.) Merr. with *Bacillus subtilis* (Suzuki *et al*. 2003). Urokinase is derived from human urine. Streptokinase, nattokinase, and urokinase were reported to possess significant fibrinolytic activity by using the fibrin plate method (Dubey *et al*. 2011). Staphylokinase is produced from *Staphylococcus aureus* and transforms inactive plasminogen into active plasmin (Silence *et al*. 1993). Bafibrinase, a new fibrinolytic serine protease enzyme, is derived from *Bacillus* sp. and has thrombolytic and anticoagulant effects (Mukherjee *et al*. 2012).

Many *in vitro* studies have been conducted on the mentioned activities of several plant extracts. By taking the most direct process into account, we summarize the medicinal plants that affect the cascades on the formation and degradation of thrombin and fibrin (Table 1). For instance, *Arnebia euchroma* (Royle) I.M.Johnst. extract decreased TT, so it can be used as a hemostatic agent (Ablat *et al*. 2021). *Syzygium cumini* (L.) Skeels leaf extracts remarkably increased PT and PTT;

therefore, it can prevent cardiovascular diseases due to its antiplatelet and anticoagulant effects (Rehman *et al*. 2019). The optical aggregation method was used to test the activity of plant extracts of *Enteromorpha clathrata* (Roth) Grev. (Qi *et al*. 2012), *Rheum* species (Seo *et al*. 2012), and *Allium cepa* L. (Jung *et al*. 2002). These plants were reported to be effective as anticoagulant agents. When the experiment of labeling the fibrinogen method was examined, *Allium sativum* L. and *Ginkgo biloba* L. extracts were found to display high potential activity on fibrinolysis at 10 µg/µL concentration (Ansari *et al*. 2011, Naderi *et al*. 2005). *Morinda citrifolia* L. extract possesses fibrinolysis activity in the ECLT testing method (Murata *et al*. 2014). *Dimocarpus longan* Lour. ethyl acetate extract is efficient in melting the fibrin zone according to Nguyen *et al*. (2021).

The plant-derived bioactive components with antiplatelet, anticoagulant, thrombolytic, clot-lysis, hemostatic, and fibrinolytic activities affect the thrombin and fibrin formation/destruction mechanism. It has been observed in *in vitro* studies that the plant-derived substances display serine protease enzyme activities in the fibrinolytic system. The secondary metabolites including bufadienolides, cyanidin, epigallocatechin gallate (EGCG), ellagic acid, aesculin, hypericin, hyperoside, myricetin, rutin, salicin, sennoside A, sennoside B, silybin, quercetin showed fibrinolytic activity by inhibiting thrombin, elastase, urokinase, trypsin, and plasmin successfully at micromolar concentrations (Sartor *et al.* 2002, Jedinák *et al.* 2006, Mozzicafreddo *et al.* 2006, Mozzicafreddo *et al.* 2008, Viskupicova *et al.* 2011, Bijak *et al.* 2013, Kolodziejczyk-Czepas *et al.* 2017).

Table 1. *In vitro* fibrinolytic, anticoagulant and thrombolytic effects of plant extracts.

Plant name	Parts used	Dose	Extract Type	Test	Activity	References
Actinidia deliciosa (A.Chev.) C.F.Liang & A.R.Ferguson	Fruit	50 µL (100 mg/mL)	70% Ethanol	Fibrin plate method	Fibrinolytic	Jung *et al*. 2005
Adhatoda vasica Nees	Root	5 mg/mL	Methanol	Clot lysis testing	Thrombolytic	Hussain *et al*. 2014
Alstonia scholaris (L.) R. Br.	Bark	100 µL (10 mg/mL)	Methanol	Clot lysis testing	Thrombolytic	Khan *et al*. 2020
Angelica acutiloba (Siebold & Zucc.) Kitag.	Root	500 mg/kg	50% Ethanol	Euglobulin lysis test	Fibrinolytic	Fukuda *et al*. 2009
Angelica acutiloba (Siebold & Zucc.) Kitag.	Root	10 mg/mL	Methanol	Fibrin plate method, Euglobulin lysis test	Fibrinolytic	Fukuda *et al*. 2009
Artemisia princeps Pamp.	-	-	%70 Ethanol	PT, aPTT	Antithrombotic	Kim *et al*. 2019
Asphodelus tenuifolius Cav.	Whole	1, 3, 5, and 10 mg/mL	Aqueous: methanol (30:70)	Clot lysis testing	Antithrombotic and thrombolytic	Gul *et al*. 2022
Averrhoa bilimbi L.	Leaf	50 mg/kg	Ethanol	Euglobulin lysis test	Activators of the fibrinolysis	Almarshad 2019
Bischofia javanica Blume	Leaf	0.1 mL	Methanol	Clot lysis testing	Thrombolytic	Chowdhury *et al*. 2020
Callistemon citrinus (Curtis) Skeels	Leaf	2 mg/100 µL water	Methanol	Clot lysis testing	Thrombolytic	Ahmed & Rahman 2016
Canna edulis Ker Gawl.	Rhizome	Ethyl acetate fraction 1 mg/mL	96% Ethanol	Optical aggregation	Antiplatelet	Nguyen *et al*. 2020
Canna edulis Ker Gawl.	Rhizome	50 µL	96% Ethanol	PT, aPTT, TT	Anticoagulant	Nguyen *et al*. 2020
Canna x generalis L.H Bailey & E.Z Bailey	Leaf, stem, and flower	50 µL	96% Ethanol	Optical aggregation	Antiplatelet	Le *et al*. 2022
Celastrus orbiculatus Thunb.	Fruit	0.40 g/kg	75% Ethanol	PT, TT	Anticoagulant	Zhou *et al*. 2019
Chlorella vulgaris Beijerinck	-	1834.6 U mg^{-1}	Tris-HCl	Fibrin plate method	Thrombolytic	da Costa e Silva *et al.* 2018
Cydonia oblonga Mill.	Leaf	20 mg/kg	Aqueous	Euglobulin lysis test	Anti-thrombotic activity	Zhou *et al*. 2014
Dendropanax morbifera Leveille	Leaf	50 mg (Rutin)	80% Ethanol	Labeling the fibrinogen	Antithrombotic	Choi *et al*. 2015
Dillenia pentagyna Roxb. and fungal isolates	Bark	500 µg/mL	Ethyl acetate	Clot lysis testing	Clot lysis activity	Chowdhury *et al*. 2022
Drynaria quercifolia (L.) J. Sm.	Rhizome	100 µL (2 mg/100 µL of water)	Methanol	Clot lysis testing	Thrombolytic	Chaity *et al*. 2016

Table 1. *In vitro* anticoagulant and thrombolytic effects of plant extracts (Continued).

Plant name	Parts used	Dose	Extract Type	Test	Activity	References
Erigeron breviscapus (Vaniot) Hand.-Mazz.	Whole plant	3.6, 7.2, 10.8 mL/kg	Herba Erigerontis injection (aqueous solution)	PT	Anticoagulant	Jiang *et al*. 2021
Fagonia arabica L.	Aerial parts	100 mg/10 mL	Methanol: isopropyl alcohol: acetone	Fibrin plate method	Clot lysis activity	Chourasia *et al*. 2011
Feijoa sellowiana (O.Berg) O.Berg.	Leaf	200 mg/kg	70% Ethanol	PT, aPTT	Anticoagulant	Amer *et al*. 2023
Flammulina velutipes	Whole mushroom	10 µL (Fibrinolytic protease)	Tris-HCl	Fibrin plate method	Fibrinolytic	Park *et al*. 2007
Fumaria officinalis L.	Aerial part	50 µL	Metanol	PT, aPTT	Anticoagulant	Edziri *et al*. 2020
Glycine max (L.) Merr. (fermented with *Bacillus subtilis)*	-	23 g of natto extract/kg (100,000 CU of nattokinase)	Aqueous	Euglobulin lysis test	Fibrinolytic	Suzuki *et al*. 2003
Haloxylon griffithii (Moq.) Boiss.	Fresh growing shoots, roots and leaf	100 µg/mL	Ethanol	Clot lysis testing	Thrombolytic	Kamal *et al*. 2021
Heritiera fomes Buch.-Ham.	Leaf, bark, and root	100 µL	Ethanol	Clot lysis testing	Thrombolytic	Ripa *et al*. 2022
Homalomena aromatica (Spreng.) Schott	Leaf	100 µL (10 mg/mL)	Methanol	Clot lysis testing	Thrombolytic	Ali *et al*. 2021
Jatropha gossypiifolia L.	Leaf	10 µL (2 µg/µL)	Aqueous	aPTT	Anticoagulant	Félix-Silva *et al*. 2014
Justicia procumbens L.	Whole plant	IC_{50}: 0,1202	75% Ethanol	Optical aggregation	Antiplatelet	Liu *et al*. 2022
Lagerstroemia speciosa (L.) Pers.	Flower	100 µL (10 mg/mL water)	Methanol	Clot lysis testing	Thrombolytic	Sharmin *et al*. 2018
Licania rigida Benth.	Leaf	50 µg/mL	Ethanol	PT, aPTT	Anticoagulant	Duarte da Luz *et al*. 2021
Meriandra dianthera (Roth ex Roem. & Schult.) Briq.	Leaf	5,10 mg/mL	Aqueous	aPTT	Anticoagulant	Kiflemariam *et al*. 2022
Merremia vitifolia (Burm.f.) Hallier f.	Leaf	100 µL	Methanol	Clot lysis testing	Thrombolytic	Akter *et al*. 2021
Millettia peguensis Ali	Leaf	100 µL	Methanol	Clot lysis testing	Thrombolytic	Alam *et al*. 2020
Morinda citrifolia L.	Fruit	200 µg/mL (Butanol soluble fraction)	50% Ethanol	Fibrin plate method	Fibrinolytic	Murata *et al*. 2014
Nelumbo nucifera Gaertn.	Fruit	100 mg/kg	98% Ethanol	PT, TT, aPTT,	Anticoagulant	Rajput *et al*. 2019
Panax japonicus (T.Nees) C.A.Mey.	Rhisome	50, 200, 500 mg/kg	70% Methanol	Euglobulin lysis test	Fibrinolytic	Matsuda *et al*. 1989
Pleurotus ostreatus	Whole mushroom	20 µL	-	Fibrin plate method	Fibrinolytic	Petraglia *et al*. 2022
Pleurotus ostreatus	Whole mushroom	10 µL (Fibrinolytic protease)	Freeze-thaw treatment, ammonium sulfate precipitation	Fibrin plate method	Fibrinolytic	Liu *et al*. 2014
Polygonum multiflorum Thunb.	-	100 mg/mL	50% Ethanol-water	Optical aggregation	Antiplatelet	Li *et al*. 2019
Spirodela polyrrhiza (L.) Schleid.	Leaf	0,4 mL	Tris-HCl	PT, aPTT, TT	Anticoagulant	Choi & Sa 2001

Table 1. *In vitro* anticoagulant and thrombolytic effects of plant extracts (Continued).

Plant name	Parts used	Dose	Extract Type	Test	Activity	References
Spirodela polyrrhiza (L.) Schleid.	Aerial parts	15 µL (Fibrinolytic protease)	Tris-HCl	Fibrin plate method	Fibrinolytic	Choi & Sa 2001
Sterculia foetida L.	Seed	100 µL	Methanol	Clot lysis testing	Thrombolytic	Alam *et al*. 2021
Syzygium aromaticum (L.) Merr. & L.M.Perry	Chitosan functionalized-silver nanoparticles	0.025 mg/kg and 0.05 mg/kg	Ethanol	PT, aPTT	Anticoagulant	Asghar *et al*. 2020
Syzygium cumini (L.) Skeels	Leaf	-	Methanol	PT	Anticoagulant	Ahmed *et al*. 2019
Tetracera sarmentosa (L.) Vahl	Leaf	100 µL	Ethanol	Clot lysis testing	Thrombolytic	Uddin *et al*. 2018
Thymus atlanticus (Ball) Pau	Leaf	10 µg/mL	Aqueous extract and polyphenol fraction	TT, PTT, aPTT	Anticoagulant	Khouya *et al*. 2020
Turnera subulata Sm.	Leaf	100 µg/mL	Ethanol/water (50:50, v/v)	PT, aPTT	Anticoagulant	Duarte da Luz *et al*. 2019

PT: Prothrombin time; APTT: Activated partial thromboplastin time; PTT: Partial thromboplastin time; TT: Thrombin time; Tris-(hydroxymethyl)-aminomethane hydrochloride; IC50: Inhibitory concentration 50; CU: Control unite.

Conclusion

In treatment approaches of peritoneal adhesion, generally used agents are the ones exerting anti-inflammatory, antioxidant, tPA, and anticoagulant activities. It can be considered that providing a fibrinolytic activity is an efficient way for repairing peritoneal adhesion. The present study aims to emphasize the importance of fibrinolytic activity in peritoneal adhesion by considering the fact that adhesion is directly correlated with fibrin formation. Indeed, fibrinolytic treatment methods have recently been very common. Since plants with thrombolytic properties facilitate blood flow, they can be evaluated as potential agents to be used in cardiovascular diseases. It has been seen that plant extracts with fibrinolytic activity are promising for intra-abdominal operations since they can be effective in preventing adhesions and further research in this area should be conducted. In addition, we consider that compounds of natural origin with anti-fibrinolytic properties can also be considered hemostatic agents. Since the pathophysiology of adhesion is associated with fibrinolytic activity, we believe that these studies will give an idea for the discovery and development of new drugs for the treatment of intra-abdominal adhesion.

Abbreviations

PDGF: Platelet-derived growth factor; TNF-α: Tumour necrosis factor-alpha; TGF-β: Transforming growth factor-beta: IL-1; Interleukin-1; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-17: Interleukin 17; IFN-γ: Interferon-γ; GM-CSF: Granulocyte-macrophage colony-stimulating factor; uPA: Urokinase-type plasminogen activator; tPA: Tissue-type plasminogen activator; PAI-1: Plasminogen activator inhibitor-1; PAI-2: Plasminogen activator inhibitor-2; α2-AP: α2-antiplasmin; ECLT: Euglobulin clot lysis time; EGF: Epidermal Growth Factor; VEGF: Vascular endothelial growth factor; IGF: Insulin-like growth factor; FGF: Fibroblast growth factor; ECM: Extracellular matrix; PT: Prothrombin time; APTT: Activated partial thromboplastin time; PTT: Partial thromboplastin time; TT: Thrombin time; TF: Tissue factor; GAGs: Glycosaminoglycans; PGs: Proteoglycans; HGF: Hepatocyte growth factor; PPP: Platelet poor plasma; FITC: Fluorescein isothiocyanate.

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