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Research Article

Study of the Acute Toxicity and Hemostatic Activity of Aqueous and Hydroethanolic Extracts of *Pavetta Crassipes*. K. schum. (Rubiaceae) Leaves

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Abstract

As part of efforts to promote traditional medicine, a scientific study was conducted on the aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves, a plant used in sub-Saharan traditional medicine. The study focused on evaluating the hemostatic potential and acute toxicity of both types of extracts. Prior to this, the phytochemical profiles of the extracts were determined using standard secondary metabolite characterization techniques described by Trevan. The results revealed that the hydroethanolic extract contains polyphenols, flavonoids, sterols, polyterpenes, saponins, and quinones. The aqueous extract contains these same compounds plus tannins. Acute toxicity testing was performed in accordance with OECD Guideline 423, and the results indicated that both extracts are non-toxic. Hemostatic activity was evaluated *ex vivo* (using rabbit blood) and *in vivo* (in rats) at concentrations of 10^{-4}, 10^{-3}, 10^{-2}, and 10^{-1} mg/mL, using phytomenadione as the reference coagulant. Activated partial thromboplastin time (aPTT), prothrombin time (PT), and bleeding time (BT) were measured for each substance. The findings showed that the aqueous extract and phytomenadione exhibited strong hemostatic activity both *ex vivo* in rabbits and *in vivo* in rats that was significantly ($p < 0.05$) greater than that of the hydroethanolic extract. Similar results were observed for prothrombin time (PT) and bleeding time (BT). Notably, this hemostatic activity was found to be dose-dependent.

Keywords: Aqueous extract, hydroethanolic extract, hemostatic, acute toxicity, *Pavetta crassipes*.

1. Introduction

Hemostasis involves a set of complex physiological mechanisms that stop bleeding following vascular injury while maintaining blood fluidity within the circulatory system[1]. Furthermore, numerous studies have demonstrated that certain medicinal plants rich in secondary metabolites specifically tannins, flavonoids, and phenolic compounds possess hemostatic, vasoconstrictive, and hematopoietic properties, thereby promoting the cessation of bleeding and the improvement of blood parameters[2,3]. Consequently, there is a growing interest in, and an urgent need for, the scientific study of medicinal plants and their use across the globe. It is against this backdrop that the plant species *Pavetta crassipes* (family Rubiaceae) was selected for this study. This plant is used in certain regions of Côte d'Ivoire notably the Poro region to treat bleeding, general fatigue, and various blood-related disorders. However, despite its widespread use, no scientific studies have been conducted to evaluate its efficacy regarding hemostasis. The present study aims to address this gap by investigating the hemostatic potential and acute toxicity of aqueous and hydroethanolic extracts derived from *Pavetta crassipes* leaves.

2. Materials and Methods

2.1. Materials

2.1.1. Plant material

For the study of the hemostatic and antianemic potential of *Pavetta crassipes*, the plant material consisted of leaves harvested in the Poro region (northern Côte d'Ivoire) and identified at the National Floristic Center of Côte d'Ivoire (CNF) under the identification number OAT-PaCr. The leaves were dried away from light and then ground into a powder, which

was used to prepare aqueous and hydroethanolic extracts.

2.1.2. Animal material

Albino rats (Rattus norvegicus), Wistar strain, of both sexes (male and female) and four months of age, weighing between 117 and 120.8 g, were used for the *in vivo* study. These animals were obtained from the animal facility of the UFR of Biological and Pharmaceutical Sciences at Félix Houphouët-Boigny University. Similarly, rabbits (*Oryctolagus cuniculus*) of both sexes (male and female) and eight months of age, weighing between 3.8 kg and 4.5 kg, were used for the *in vitro* study. These animals were also obtained from the animal facility of the UFR of Biological and Pharmaceutical Sciences at Félix Houphouët-Boigny University.

2.2. Methods

2.2.1. Sampling and production of *Pavetta crassipes* powder

For our study, the plant material consisted of 5 kg of leaves. The leaves were selected for harvesting due to the easy access to and abundance of *Pavetta crassipes* in the area. The leaves were harvested in Sinématiali, stored in biodegradable bags, and transported by van immediately after harvesting. The material was kept in an oven for three weeks before being ground using a mechanical grinder (IKAMAG, Japan).

2. 2.2. Preparation of extracts

Leaves from the *Pavetta crassipes* plant are used to assess hemostatic potential. The leaves are dried and then ground into a powder. 100 g of the dried leaf powder is placed in one liter of water and boiled for 15 minutes before being filtered through Whatman filter paper. The resulting filtrate is oven-dried at 40°C for one week to obtain the aqueous extract of *Pavetta crassipes* leaves. The method described by[4] is used to obtain the 70% hydroethanolic extract of *Pavetta crassipes* leaves. To do this, a 70% hydroethanolic solution (70:30 ethanol/water) is used to prepare the extract in flasks, utilizing one liter of the solution and 100 g of the plant's leaf powder. The resulting mixture is homogenized using a magnetic stirrer for 24 hours. The homogenate is filtered through Whatman filter paper, followed by vacuum filtration for one hour. The collected filtrate is concentrated using a rotary evaporator and then oven-dried at 40°C for one week to ensure complete drying, yielding the 70% hydroethanolic extract. After drying, the hydroethanolic extract of *Pavetta crassipes* leaves appears as a dark green paste, whereas the aqueous extract appears as a dry brown powder.

2.2.3. Phytochemical study of the extracts

The phytochemical study was conducted on the 70% hydroethanolic extract and the aqueous extract of *Pavetta crassipes* leaves, using standard characterization reactions for chemical groups. These groups included polyphenols, flavonoids, polyterpenes, quinones, tannins, and saponins, analyzed using the methods described by[5]. The presence of sterols and polyterpenes was determined via the Liebermann reaction. Polyphenolic compounds were detected using the ferric chloride reaction. Flavonoids were identified using the cyanohydrin reaction. The detection of saponins was based on their foaming property upon agitation. The presence of quinones was confirmed by a color change to yellow following the addition of a few drops of NaOH. Finally, tannins were detected using the ferric chloride reaction, and alkaloids were identified using Dragendorff reagent.

2.2.5. Acute toxicity study of the two types of extracts

The acute toxicity study was conducted in accordance with OECD Guideline 423[6].

A 0.9% sodium chloride (NaCl) solution was used to prepare the various concentrations of *Pavetta crassipes* extracts. Extract concentrations were prepared based on the mean weight of the female rats and the dosage (mg/kg body weight). The mean weight of the female rats was 120.9 ± 0.07 g. The animals were fasted for 24 hours prior to the administration of the various doses of *Pavetta crassipes* extracts and the NaCl solution. For an injection dose of 100 mg/kg body weight, a 1 mL volume of each extract solution and the saline solution was injected into each group of female rats. Group 1 (the control group) received the 0.9% NaCl solution. Groups 2, 3, and 4 received doses of 300, 2000, and 5000 mg/kg, respectively, of the 70% hydroethanolic extract of *Pavetta crassipes* leaves. Similarly, groups 5, 6, and 7 received doses of 300, 2000, and 5000 mg/kg, respectively, of the aqueous extract of *Pavetta crassipes* leaves. The treated animals were monitored continuously for 14 days, with particular attention paid during the first 24 hours to record clinical signs and mortality in each group.

2.2.6. Study of hemostatic activity

These tests were conducted *in vitro* using blood plasma from a healthy adult male rabbit and *in vivo* using rats, testing aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves alongside vitamin K1. These tests, designed to evaluate the intrinsic and extrinsic coagulation pathways, were performed according to the method described by[7].

2.2.7. Preparation of platelet-poor plasma (PPP)

Platelet-poor plasma was prepared using the method described by the professional order of medical technicians of Quebec[8]. The platelet-poor plasma was obtained two hours after blood collection. Citrate tubes containing the blood were centrifuged at 2.500 rpm for 15 minutes. The centrifuged plasma was collected and transferred to a vial, leaving approximately half a centimeter of plasma above the cellular layer (composed of red blood cells, platelets, and white blood cells). The vial was then centrifuged at 2.500 rpm for 10 minutes. The plasma was collected a second time avoiding the bottom of the tube where cellular debris had settled to yield the platelet-poor plasma.

2.2.8. Test to evaluate the intrinsic or endogenous coagulation pathway (aPTT)

The principle of this test involves measuring plasma coagulation time following recalcification[9]. Mixtures consisting of 47 µL of plasma and 7 µL of each extract type (aqueous and hydroethanolic) from *Pavetta crassipes* leaves as well as vitamin K1 at concentrations of 10^{-4}, 10^{-3}, 10^{-2}, and 10^{-1} mg/mL were prepared in separate test tubes. These tubes were incubated in a water bath at 37°C for 5 minutes. Concurrently, 50 µL plasma samples were incubated in a water bath at 37°C for 2 minutes and then added to the previously prepared mixtures in each tube. These tubes were re-incubated at 37°C for 3 minutes, and coagulation was triggered by adding 50 µL of a 0.005 M aqueous calcium chloride solution. Coagulation time was then determined using a coagulometer, measuring from the moment the calcium chloride was added. A separate test tube containing plasma served as a control and received no extract or vitamin K1.

2.2.9. Test for the extrinsic (or exogenous) coagulation pathway (PT)

Volumes of 47 µL of plasma were placed into cuvettes used for coagulation testing. To these plasma aliquots, 7 µL of each extract type (aqueous and hydroethanolic) from *Pavetta crassipes* leaves as well as vitamin K1 were added at concentrations of 10^{-4}, 10^{-3}, 10^{-2}, and 10^{-1} mg/mL. These tubes were incubated at 37°C for 5 minutes. Subsequently, 50 µL of prothrombin reagent (rabbit blood and calcium chloride), preheated to 37°C for 30 minutes, was added to the mixture

in each tube. The coagulation time was recorded using a coagulometer. A separate tube containing plasma served as a control and received no extract or vitamin K1.

2.2.10. Evaluation of aqueous and hydroethanolic extracts on bleeding time (BT)

The rat tail hemorrhage model is one of the most widely used models for preclinical studies on the efficacy of hemostatic agents[10]. The *in vivo* hemostatic activity of aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves was investigated as described by[11]. To this end, twenty-four rats of both sexes were divided into four groups of six rats each.

- Group 1 received distilled water (control) for four days.

- Group 2 received phytomenadione (at 15 mg/kg body weight for four days).

- Group 3 received the hydroethanolic extract at 200 mg/kg body weight for four days.

- Group 4 received the aqueous extract at 200 mg/kg body weight for four days.

Rats in each group were anesthetized with ketamine (100 mg/kg body weight), and the tip of the tail was cut to induce bleeding. The bleeding site was blotted with filter paper every thirty seconds until bleeding stopped. The time taken for bleeding to cease was recorded. Care was taken to ensure that no pressure was applied to the tail tip that could affect hemostasis.

2.3. Statistical analyses

Results were expressed as the mean ± standard deviation (SD). Data presentation and analysis were performed using GraphPad Prism 5.0 software (Microsoft, USA). Differences between means were determined using Dunnett's test: $p<0.01$ (highly significant difference) and $p<0.05$ (significant difference).

3. Results and Discussion

3.1. Results

3.1.1. Phytochemical screening

Phytochemical screening revealed that the hydroethanolic extract of *Pavetta crassipes* leaves contains polyphenols, flavonoids, sterols, polyterpenes, quinones, and saponins. However, it does not contain tannins or alkaloids. As for the aqueous extract, in addition to the chemical compounds mentioned above, it contains tannins **(Table I).**

3.1.2. Acute toxicity

Following the administration of the two types of *Pavetta crassipes* extracts to female rats at doses of 300, 2000, and 5000 mg/kg of body weight, no significant changes in their behavior were observed. Furthermore, no mortality was recorded during the 14 days observation period **(Table II).**

3.1.3. Study of the hemostatic potential of aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves

3.1.3.1. Effect of aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves and phytomenadione on activated partial thromboplastin time (aPTT)

Testing the intrinsic (or endogenous) coagulation pathway revealed the effects of the aqueous and hydroethanolic extracts and phytomenadione (vitamin K1) on coagulation **(Figure 1).** At a concentration of 10^{-4} mg/mL, the aqueous extract and phytomenadione caused a highly significant reduction in activated partial thromboplastin time ($p < 0.01$) compared to the hydroethanolic extract, and an even more significant reduction compared to the control (blood without added substances) ($p < 0.001$), with the following respective values: 7.11 ± 0.51S for the aqueous extract; 7.01 ± 0.53S for phytomenadione; 19.01 ± 0.13S for the hydroethanolic extract; and 20.55 ± 0.33S for the control. Furthermore, at a concentration of 10^{-3} mg/mL, the aqueous extract and phytomenadione caused a highly significant reduction in the activated partial thromboplastin time ($p < 0.01$) compared to the hydroethanolic extract, and an even more significant reduction compared to the control (blood without additives) ($p < 0.001$), with the following respective values: 6.87 ± 0.57S for the aqueous extract, 6.77 ± 0.40S for phytomenadione, 17.2 ± 0.17S for the

hydroethanolic extract, and 20.55 ± 0.33S for the control. However, there was no significant difference between the hydroethanolic extract and phytomenadione regarding this reduction in activated partial thromboplastin time ($p > 0.05$). Similar results were observed at concentrations of 10^{-2} mg/mL and 10^{-1} mg/mL for each type of substance. Notably, this reduction was particularly pronounced at the 10^{-1} mg/mL concentration. This decrease in activated partial thromboplastin time is dose-dependent; that is, as the concentration increases, the activated partial thromboplastin time decreases.

3.1.3.2. Effect of aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves and phytomenadione on prothrombin time (PT)

The test assessing the extrinsic (or exogenous) coagulation pathway demonstrated the effects of the aqueous and hydroethanolic extracts and phytomenadione (vitamin K1) on coagulation **(Figure 2).** At a concentration of 10^{-4} mg/mL, the hydroethanolic extract, the aqueous extract, and phytomenadione did not cause a significant reduction in prothrombin time ($p > 0.05$) compared to the control, with the following respective values: 21.35 ± 0.17S for the aqueous extract; 20.01 ± 0.15S for phytomenadione; 21.01 ± 0.11S for the hydroethanolic extract; and 21.8 ± 0.41S for the control. Similarly, at a concentration of 10^{-3} mg/mL, the hydroethanolic extract, the aqueous extract, and phytomenadione did not cause a significant reduction in prothrombin time ($p > 0.05$) compared to the control (blood without added substances), with the following respective values: 21.07 ± 0.33S for the aqueous extract; 20.07 ± 0.30S for phytomenadione; 21.2 ± 0.18S for the hydroethanolic extract; and 21.8 ± 0.41S for the control. The same observation was made at concentrations of 10^{-2} mg/mL and 10^{-1} mg/mL for each type of substance. This test revealed that prothrombin time was not affected by the application of the two types of extracts and phytomenadione.

Table I: Phytochemical screening of the hydroethanolic extract of *Pavetta crassipes* leaves

	Alkaloids	sterols, and polyterpenes	Polyphenols	Flavonoids	Tannins	Quinones	Saponins
Hydroethanolic extract	-	+	+	+	-	+	+
Aqueous extract	-	+	+	+	+	+	+

+ : Presence - : Absence

Table II: Clinical signs and mortality observed following administration of the hydroethanolic extract and the aqueous extract of *Pavetta crassipes* leaves

	Hydroethanolic extract and aqueous extract		
Injected doses (mg/kg) bw	300	2000	5000
Abdominal constrictions	-	-	-
Immobility	-	-	-
Rapid breathing	-	-	-
Paralysis of the limbs	-	-	-
Nutrition	+	+	+
Animals mortality	0	0	0

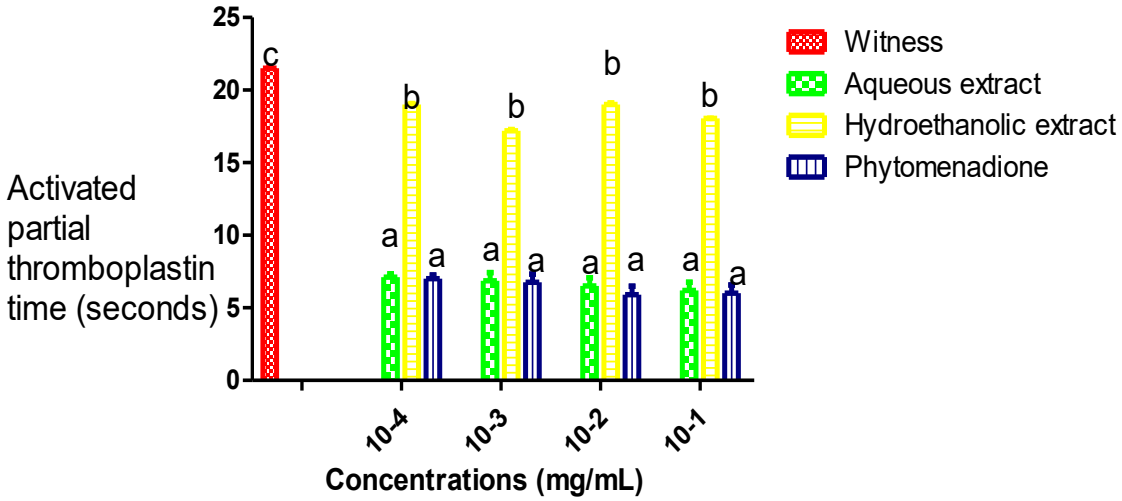

Figure 1: Effect of aqueous extracts, hydroethanolic extract and phytomenadione on activated partial thromboplastin time (aPTT)

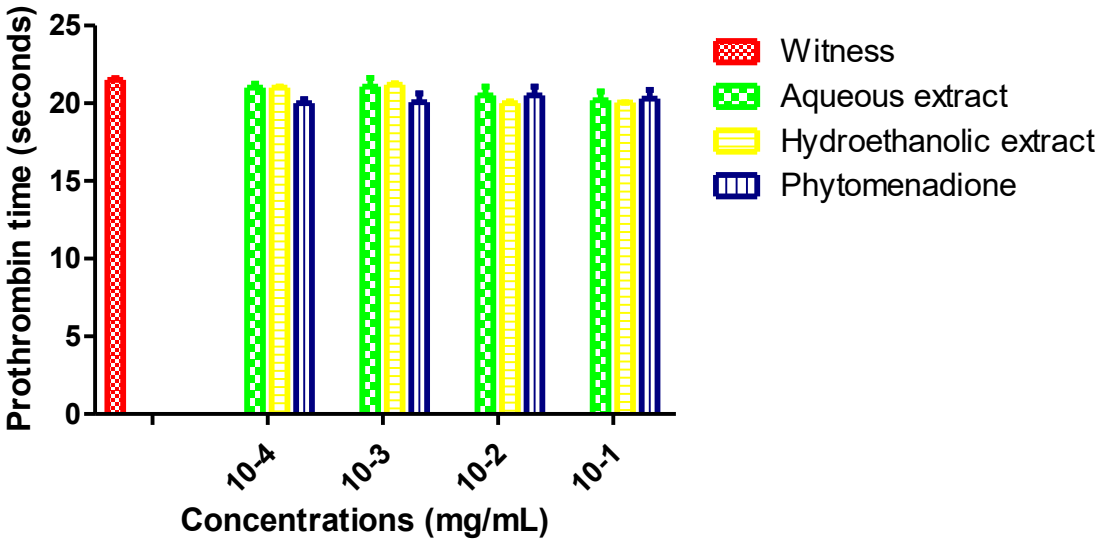

Figure 2: Effect of aqueous extracts, hydroethanolic extract and phytomenadione on prothrombin time (PT)

3.1.3.3. Effect of aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves and phytomenadione on bleeding time (BT)

Figure 3 shows the effect of aqueous and hydroethanolic extracts of *Pavetta crassipes* leaves and phytomenadione (a coagulant vitamin) on bleeding time. The control bleeding time was 24.24 ± 0.45 seconds. Bleeding time was shortened in rats treated with the aqueous extract (200 mg/kg bw) and phytomenadione (100 mg/kg bw) compared to rats treated with the hydroethanolic extract (200 mg/kg bw) and untreated rats (control). Bleeding times were, respectively: 7.47 ± 0.75S for the aqueous extract; 6.85 ± 0.75S for phytomenadione; 13.55 ± 0.75S for the hydroethanolic extract; and 24.24 ± 0.45S for the control. This shortening was significant with the hydroethanolic extract and phytomenadione compared to the aqueous extract ($p < 0.05$) and highly significant compared to the control ($p < 0.001$). Furthermore, there was no significant difference between the extract hydroethanolic and phytomenadione regarding bleeding time ($p > 0.05$).

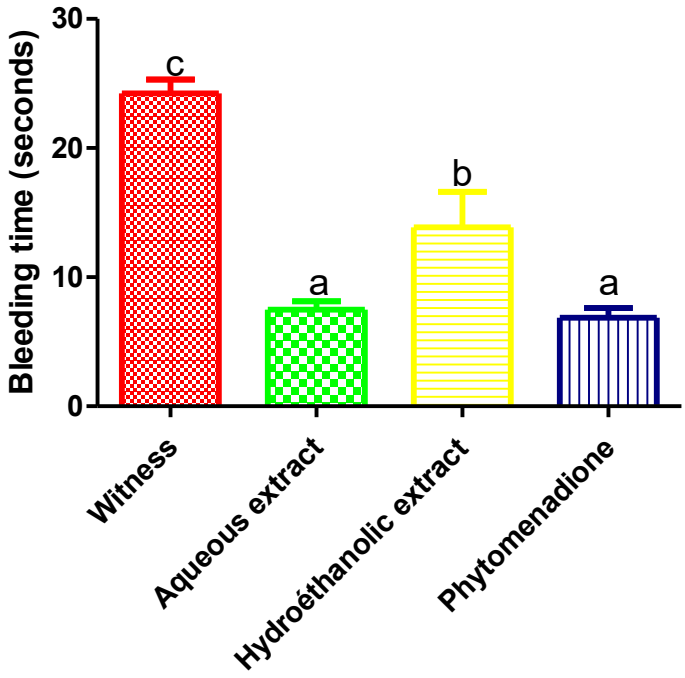

Figure 3: Effect of aqueous extract, hydroethanolic extract and phytomenadione on bleeding time (BT) *in vivo*

4. Discussion

Phytochemical analysis revealed certain chemical compounds in the hydroethanolic and aqueous extracts of *Pavetta crassipes* leaves. The main active compounds identified are polyphenols, flavonoids, sterols, polyterpenes, quinones, and saponins. This is consistent with the work of[12] in their phytochemical screening of *Lawsonia inermis*, which showed that the leaves contain the compounds mentioned above. Similarly, the results are consistent with those found by[13] on *H. ledifolium*. However, the aqueous extract also contains tannins, a result that is consistent with that of[14] on *Pavetta crassipes* leaves. The presence of these metabolites would indicate biological activities[15]. Numerous studies have indicated that flavonoids possess analgesic properties capable of regulating immune system function[16]. Furthermore, many flavonoids are capable of reducing the production of reactive oxygen species[17]. Among antioxidants, polyphenols are thought to react with most reactive oxygen species. Similarly, flavonoids are also thought to react with most reactive oxygen species[18]. Regarding mortality, no deaths were observed at doses of 300, 2000, and 5000 mg/kg wt with the hydroethanolic and aqueous extracts of *Pavetta crassipes* leaves. The non-toxicity of the hydroethanolic extract could be explained by the fact that the mixture of water and ethanol did not dissolve a large quantity of toxic substances[4]. Similarly, the non-toxicity of the aqueous extract could be explained by the fact that the mixture of *Pavetta crassipes* powder and distilled water did not dissolve toxic substances stored in mucilage-containing cells[4]. The absence of tannins in the hydroethanolic extract could be related to the extraction conditions or the polarity of the solvent used[3]. Thus, the Globally Harmonized System (GHS) according to[6] classifies both types of *Pavetta crassipes* leaf extracts in category 5 and defines them as non-toxic according to the[19]in rats. Furthermore, *in vivo* and *ex vivo* coagulation studies demonstrated the effect of aqueous and hydroethanolic extracts of *Pavetta crassipes*, as well as phytomenadione (vitamin K1), on coagulation. Both hydroethanolic and aqueous extracts of *Pavetta crassipes*, at increasing concentrations, and phytomenadione caused a significant shortening of the activated partial thromboplastin time (aPTT) *ex vivo.* However, the aqueous extract and phytomenadione resulted in a significantly shorter aPTT compared to the hydroethanolic extract. This shortening of the time was dose-dependent on the extract. Similarly, the aqueous extract and phytomenadione significantly shortened bleeding time compared to the hydroethanolic extract. However, prothrombin time was not affected by either type of extract. Therefore, the aqueous extract accelerates plasma coagulation, just like vitamin K1. The aqueous extract may act via the intrinsic coagulation pathway, which involves plasma proteins, factors VIII, IX, XI, and XII, and prekallikrein[20]. This finding is a promising indication of hemostatic and astringent properties for the aqueous extract. This astringent activity would promote vasoconstriction, a crucial factor in hemostasis. The effectiveness of the aqueous extract of *Pavetta crassipes* on hemostasis is due to the presence of tannins in the extract[14], unlike the hydroethanolic extract, which does not contain them. These results are consistent with those found by[21]. Similarly, this result is consistent with that of[3], who studied the aqueous and hydroethanolic extracts of the leaves of four medicinal

plants commonly sold by herbalists in Benin to treat bleeding: *Cassytha filiformis* and *Cissampelos mucronata*. Indeed, tannins have hemostatic and vasoconstrictive properties on small vessels, and are also used to treat varicose veins and other conditions.

5. Conclusion

The results obtained in this study showed that both the hydroethanolic and aqueous extracts of *Pavetta crassipes* leaves are non-toxic and contain secondary metabolites such as polyphenols, flavonoids, sterols, polyterpenes, quinones, saponins, and tannins. Furthermore, this study demonstrated that the aqueous extract of *Pavetta crassipes* leaves possesses pronounced hemostatic properties compared to the hydroethanolic extract. These results provide a scientific basis for the traditional use of *Pavetta crassipes* leaves in the management of various ailments.

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Author's contribution: All authors contributed to the conception, execution, financing of this project and its publication.

Ethics approval: The experimental procedures and protocols used in this study were approved by the ethics committee, Health Sciences Committee, Félix Houphouët-Boigny University. These guidelines were in accordance with those of the European Council Legislation 87/607/EEC for the protection of experimental animals. Every effort has been made to minimize animal suffering and reduce the number of animals used.

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