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Research Paper

ACTION OF ETHYL EXTRACT OF *Ficus umbellata* LEAVES ON BLOOD COAGULATION IN WISTAR RATS

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Abstract

The main objective of our research is to determine the action of ethyl extract of *Ficus umbellata* leaves on blood coagulation in wistar rats. To do this, an extraction using 50g powder of dried leaves of *F. umbellata* and 500ml of ethanol was first performed. Then our study was carried out on 12 male and female Wistar rats aged 10 to 12 weeks and weighing between 100 and 200 g. These animals were raised at the FAST Biomembrane and Cellular Signaling Laboratory at UAC under standard environmental conditions. The animals have free access to water and food. 12 rats were randomly arranged in 4 groups of 3 and were given different doses of the ethyl extract of *ficus umbellata* leaves for a period of 7 days. Each group was subjected to the following treatment respectively: fed with distilled water, fed with 50 mg/kg bw of *F. umbellata* extract, fed with 100 mg/kg bw of *F. Umbellata*, and fed with 200mg/kg bw. The weight changes of the rats during the treatment were measured. After 7 days of treatment, the blood of the rats was collected for a bleeding time experiment, a clotting time experiment, and the determination of some blood parameters (platelet count, prothrombin level). The results of the phytochemical screening carried out on the powder of the leaves of *F. umbellata* reveal the presence of several chemical compounds such as flavonoids, alkaloids, tannins, cardiotoxic heterosides, mucilages. But in variable proportions. After 7 days of treatment, evaluation of the effect of the extract on the body weight of rats showed that the weight of control rats increased well while that of rats treated with the dose of (50; 100 and 200 mg/kg) decreased. Furthermore, the effect of ethyl extract of *F. Umbellata* leaves on blood coagulation was studied to verify that the said extract can be used to manage bleeding. This was done by examining the action of the extract on bleeding time, clotting time, platelet count, and prothrombin level.

Key words: *Ficus umbellata*, *ethanolic*, *blood coagulation*, *extracts*, *TS TC*, *TP*.

INTRODUCTION

Medicinal plants represent a valuable resource for the majority of rural and urban populations in Africa and are the primary means by which individuals heal themselves (Badiaga, 2011). With the advancement of pharmacology, the traditional therapeutic use of medicinal plants is very present in several countries of the world and especially in developing countries (Tabuti *et al.*, 2003). These medicinal plants are widespread in the African forests and savannahs and have been used for several millennia as the sole means of treatment by the African peoples of old (Tchigankong, 2009). The knowledge of the species due to their use in traditional herbal medicine is a big step towards a better exploitation of these resources. It allows us to know which species should be prioritized for research to discover new molecules (Okou, 2009). Today, according to the World Health Organization (WHO), nearly 80% of populations depend on traditional medicine for primary health care. Considerable economic benefits in the development of traditional medicine have been noted. The study of plant chemistry is still very relevant despite its age. This is mainly due to the fact that the plant kingdom represents an important source of an immense variety of bioactive molecules (Ferrari, 2002).

Plants can be considered libraries of small molecule secondary metabolites of organic compounds with a structural diversity that might not otherwise be available in a chemical synthesis laboratory (Bindseil *et al.*, 2001; Koehn and Carter, 2005).

The African continent is one of the continents with the richest biodiversity in the world.

In West Africa, as in the rest of the continent, more than 80% of the population relies on traditional medicine and medicinal plants for their primary health care. The lack of essential drugs, the inadequacy of health care, the high cost of drugs and the socio-cultural habits of the populations explain the use of traditional practices based on medicinal plants (Sanogo *et al.*, 2006). Moreover, the effectiveness of the recipes in the treatment of several pathologies makes them more interesting than modern synthetic molecules (Ali *et al.*, 2001). In this context, the use of medicinal plants as a second recourse to the discovery of new compounds by modern medicine must be taken into account. Knowing, improving and enhancing the use of medicinal plants is an urgent and permanent need. In the same perspective, the fig tree has been the subject of

several studies where its usefulness both in the field of traditional medicine and the food field was revealed. *Ficus umbellata* is used in traditional medicine as a woman's medicine for dysmenorrhea (J. KERHANO and J-G ADAM 1964).

Still in traditional medicine *ficus umbellata* leaves is used for dystocic deliveries, stomach aches (Diop, 2006). Numerous research works have revealed the presence of several secondary metabolites in the extracts of *F. umbellata* namely flavonoids, heterosides and tannins (Ibrahima DIOUF June 2017).

In order to enhance and improve the knowledge on plants with pharmacological activity, we propose to evaluate the effect of *F. umbellata* on blood coagulation in wistar rats.

Coagulation or hemostasis is an essential phenomenon for the protection of the vascular system. It prevents excessive bleeding in the event of a cut. Coagulation must follow a balance: if it is insufficient, it can cause spontaneous bleeding (hemorrhages). On the contrary, when it is excessive, it can be associated with the formation of blood clots. These can travel through the vessels to the heart, lungs or brain and have serious consequences (deep vein thrombosis, pulmonary embolism, heart attack). *Joel L. Moake, MD, Baylor 2018.*

The present work is structured in three parts: the first one concerns the bibliographical review, the second one presents the framework, material and methods of study and the third one exposes the results and discussion.

The aim of this research is to contribute to the discovery of new molecules of plant origin in the improvement of human health by proving the action of the ethanolic extract of *Ficus umbellata* on blood coagulation. Higher plants such as *Ficus umbellata* have the capacity to synthesize, through complex metabolic pathways, numerous compounds that they use for various adaptive functions, notably in response to biotic and abiotic stresses that they may undergo. Plants therefore contain a wide variety of chemical molecules (peptides, terpenes, polyphenols, alkaloids ...) with very different physicochemical properties and which present a wide variety of biological activities (anti-tumor, antiviral, antimicrobial, antioxidant healing ...). It is also recognized today that plants are an important source of bioactive molecules. (Thomas Michel 2011). In recent years, natural substances are experiencing increasing interest in many areas.

The present work has a double interest: on the one hand, from a scientific point of view, the results of this work aim to show the role of the metabolites present in this plant in the treatment of diseases related to blood coagulation; on the other hand, these results will provide a simple and inexpensive method for access to a wider public.

The general objective of this research is to determine the action of ethyl extract of *Ficus umbellata* leaves on the different parameters of blood coagulation in "wistar" rats

II MATERIALS AND METHODS

Material

❖ Plant material

The plant material used in our work is composed of the leaves of *F. umbellata*.



Figure 1 Dried leaves of *ficus umbellata*

Source: cliché OUSSA GANSI, 2021

❖ Animal material

The experiments were carried out on adult male and female Wistar rats weighing between 150 and 350g with an omnivorous diet with a tendency to granivore with an average size of 25cm and aged between 6 and 8 weeks. 15 specimens were used for the different manipulations. Upon receipt, the rats were randomly placed in groups of (3) in standard cages for a period of acclimatization before being used in the different experiments. During this period, the animals had free access to food and water and were kept in the animal house of the laboratory of biomembrane and cell signalling of the department of physiology and application of the University of Abomey-Calai

❖ Extraction equipment

The following materials are used. These are distilled water, ethanol 90°, tooth mill, plastic funnel of hydrophilic cotton (filter) **and** vacuum pump and rotary evaporator (rotavapor). The rotavapor allows to perform the distillation in one step, quickly and in a product-friendly way. This procedure is based on the evaporation and condensation of solvent by means of a rotavapor flask under vacuum. Vacuum distillation improves the processing result and helps to protect the products.

Study methods

Drying of the leaves

The leaves of *F. umbellata* were collected in May in the vicinity of the UAC in a family concession in the city of Abomey Calavi. They were identified by the botanical experts of the National Herbarium of the University.

After harvesting, the plant material is dried in the shade (at room temperature) on a bench of the Laboratory of Biomembranes, and Cellular Signaling located at the Faculty of Science and Technology (FAST) of the University of Abomey-Calavi (UAC), for 3 months in a dry and ventilated area, in order to preserve the integrity of the bioactive molecules sought, by minimizing the various mechanisms of fermentation and degradation inherent to the organic character of this raw material.

After drying, the leaves are ground into a powder using a RETSCH brand tooth grinder and stored in glass jars to avoid the installation of polluting micro-organisms.

Extraction

➤ How it works

The objective of this step is to extract a large majority of the active compounds of our plant. The extraction is generally dictated by bibliographic information concerning the chemistry of the plant constituents. As solvent, we used ethanol. The extraction is carried out in 3 steps: maceration, filtration, evaporation

Preparation of the extract:

100 g of *F. umbellata* leaf powder are put in contact with 1000 ml of ethanol. Put in continuous agitation for 24 hours. After maceration, the macerate is filtered with filter

paper and then hydrophilic cotton placed in a funnel connected to a suction pump that accelerates the filtration. After a few minutes, an exclusively liquid solution is obtained (the operation was repeated for three consecutive times). The filtrate obtained is put in an oven at 45°C to evaporate the ethanol. Then the dried extracts will be scraped, weighed and the yield calculated.

❖ Preparation of the *Ficus umbellata* solution

Introduce 5 mg of ethanolic extract of *Ficus umbellata* leaves dissolved in 1ml of physiological water solution. This gives a stock solution of *Ficus umbellata* at 5mg/ml. The latter is vigorously shaken.

The extraction yield (R) was calculated by the formula:

$$R = (Me/Mm) * 100$$

Me = Mass of extract

Mm = Mass of dry matter (Powder)

Chemical study

The chemical study of *Ficus umbellata* shows the presence of flavonosides, heterosides and tannins.

➤ Characterization of tannins

Two types of characterization were carried out with the filtrate obtained thanks to the infusion during 30 mn of 5 g of leaf powder in 50 ml of boiling distilled water:

- The presence of tannins was revealed by a brownish-purple coloration that developed when the solution obtained was shaken by adding a few drops of FeCl₃ solution (2%) to 5ml of the filtrate;
- the presence of tannins can also be highlighted by phosphoric acid; this involves diluting the infused to 1/10th with distilled water and to 1ml of this dilution is added 1ml of phosphoric acid and 9ml of an aqueous solution of sodium carbonate at 25%; the tannins were revealed by the blue color of the mixture. Note however the existence of

two groups of tannins: hydrolysable non-condensed tannins and non-hydrolysable condensed tannins.

➤ **Characterization of flavonosides**

Flavonosides are extractable by ethyl alcohol at 96° or by hot distilled water; they are not very soluble in cold water.

Two types of characterization were used.

On the one hand, the coloring in alkaline medium: In alkaline medium, flavonosides dissolve easily by giving colorings going from yellow to brown

On the other hand, the cyanidin reaction: Flavonosides give various colorations going from orange-red to violet in alcoholic solution, in the presence of nascent hydrogen produced in situ by the action of pure hydrochloric acid on magnesium; in a test tube, 2 ml of the filtrate is put, then 2 ml of hydrochloric alcohol [96° ethyl alcohol (2 vol.) + concentrated HCl (1 vol.)] and finally some fragments of magnesium; the reaction is exothermic and a pink then red coloration is slowly developed showing the presence of flavonosides.

➤ **Characterization of cardiotoxic heterosides**

The solution obtained by putting 1g of leaf powder in a test tube with 5 ml of chloroform (4 vol.) / ethanol (1 vol.) mixture was left to macerate for 30 min while shaking the tube from time to time. Then the filtrate obtained was distributed in 3 "hemolysis tubes".

To each tube is added 0.5 ml of a reagent (Baljet, Kedde or Raymond-Marthoud reagent).

Two drops of sodium hydroxide solution diluted to 1/5 in 95° ethyl alcohol are added to each tube. After shaking and making sure that the pH is alkaline, the following colorations are observed:

tube 1 (Baljet reagent): stable orange-red if cardiotoxic heterosides are present

tube 2 (Kedde's reagent): stable red-purple if cardiotoxic heterosides are present;

tube 3 (Raymond-Marthoud reagent): fugitive violet if cardiotoxic heterosides are present. (Diop D. 2006)

Evaluation of the coagulant activity

The activity of the extract is determined by the analysis of coagulation tests

We have 12 rats divided into 4 groups of 3 rats. Weighing and blood sampling before gavage. The gavage will be done once a day during 7 days then the rats will be weighed and a blood sample will be taken for the different analyses of coagulation

Day 0: Weight taking and blood sampling for the different coagulation tests of all rats before any operation.

Day 1: Batch feeding

- Group N°1 : 3 rats, gavaged with distilled water.
- Group 2: 3 rats, dosed with 50 mg/kg bw of ethyl extract of *F. umbellata* leaves
- Group N°3 : 3 rats, gavaged with 100 mg/kg bw of ethyl extract of *F. umbellata* leaves
- Group N°4 : 3 rats, gavaged with 200 mg/kg bw of ethyl extract of *F. umbellata* leaves
- Day 7: Weight gain and feeding
- Day 8: sampling
- **Blood sampling**

The blood of the rats of batches (1-3) are all collected before treatment at D=0. Blood sampling was performed according to the experimental protocol used by (Weiss et al. 2000), and modified by (Descat; 2002). The retro-orbital sinus puncture was performed under anesthesia (diethyl ether). The anesthetized animal is held with one hand in lateral decubitus, and held by the skin of the neck. The pressure of the thumb on the neck, behind the angle of the jaw, will make it possible to carry out a compression of the jugular vein, and thus a venous stasis towards the head, supporting the filling of the retroorbital sinus. By slightly pulling on the upper eyelid with the index finger, we will create an exophthalmos facilitating blood collection with the help of a non-heparinized hematocrit tube. The tip of the tube is slowly introduced into the lateral angle of the eye. Progress through the tissue is facilitated by rotating the tube slightly. As soon as the

venous plexus is reached, the blood gushes into the periorbital space and rises by capillary action into the tube. The volume of blood collected is about 1 to 2 ml in citrated tubes. Before the tube is removed, the compression is released and the bleeding stops spontaneously when the ocular pressure normalizes. The recovered blood is used for the determination of the different parameters of hemostasis.

Coagulation test

Coagulation tests measure the ability of blood to clot, as well as the time it takes to clot.

Platelet count

The number of platelets in the blood can be determined by a platelet count and can help diagnose disorders related to a platelet defect or excess. The results are obtained quickly using automatic counters. The technique is reproducible from one device to another. In the absence of an automatic counter, it is possible to count platelets if one has a microscope, at best with phase contrast, and a gridded glass slide, known as a Malassez cell. (Charles Marc Samama* and Marianne Scholtès Bobigny, France. 10 APRIL 2002)

Normal values

150 400 g/l (150 to 400 000/mm³)

Bleeding time experience

DUKE's method: the ventral surface of the cleanly shaved rat tail was carefully cleaned with cotton swabbed in 70% ethanol and with disposable lancets, a 3mm deep laceration was made on the tail.

A drop of the extract preparation will be delivered directly into the experimental laceration. The addition will be made periodically and blotted with absorbent cotton until the bleeding stops and the time taken for the bleeding to stop will be recorded as the bleeding time. Another laceration will also be made on the tail of another rat to serve as a control and the procedure will be repeated but this time without the addition of the extract and the bleeding time is recorded.

Clotting time experiment

It is a global test performed on whole blood. Blood is collected in dry glass tubes, rinsed with saline. In each tube 1ml of freshly collected rat blood is shaken every minute at 37°C, and the stopwatch is immediately started until complete coagulation. After a few minutes the tubes will be tilted very gently to see if the blood has clotted completely. Coagulation is considered complete when the tube can be inverted without significant movement of blood in the tube. The time taken for the blood to clot in each tube will be recorded and the procedure repeated.

Determination of prothrombin levels

To measure the Prothrombin Rate, a simple blood test is sufficient, even on an empty stomach, and the result is obtained in about an hour. The prothrombin time is measured as follows:

- A sample of decoagulated plasma (citrated plasma) is brought together with a reagent (which varies from one lab to another). The reagent is calcium thromboplastin, a tissue coagulation activator;
- The time taken for plasma to clot is by definition the prothrombin time.

Determination of the activated partial thromboplastin time (tca)

It is the clotting time of a depleted citrated plasma to which an activator of the contact and cephalin factors is added. It is expressed in seconds compared to a control (normal less than 1.2 times the time of the control expressed in seconds, i.e. a time less than or equal to 36 s for a control at 30 s).

It is automatable, simple and inexpensive.

Statistical analysis

For analysis, data are measured in triplicate. Statistical analysis graphs are plotted using Excel software. The obtained data are analyzed using Student's t-test and Anova. Values of $p < 0.01$

III RESULTS

Extraction yields

The yield of the extraction is obtained by making the ratio between the mass of the extract and the mass of the leaf powder.

$$R = \left(\frac{\text{masse de l'extract}}{\text{masse de la poudre e feuille}} \right) \times 100$$

$$\text{AN: } R = \left(\frac{4.42}{100} \right) \times 100$$

$$R_m = 2.14\%$$

The extraction gave an average yield of (2.14%).

Changes in the weight of the rats during the treatment

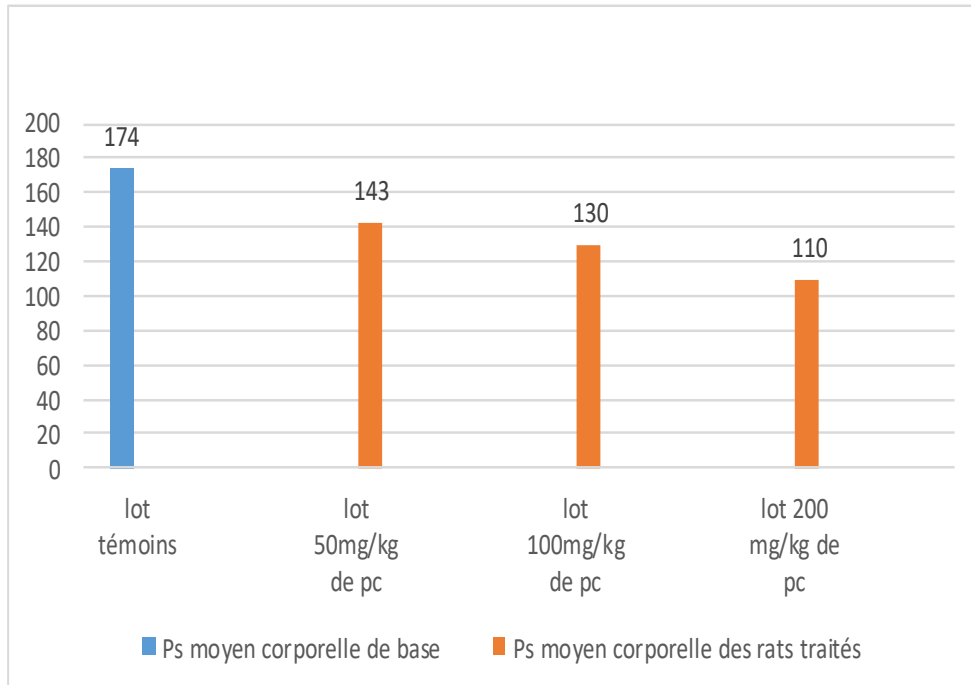


Figure 2 Growth rate analysis in normal control and ethyl extract treated rats of *F. umbellata* leaves.

Analysis of growth rate in rats during treatment is determined by weight gain each day before gavage during the allotted period. Then the average weight per dose administered is calculated to generate the above graph. From this graph, it can be seen that the weight variation decreases with the administered dose.

Determination of bleeding time

The measurement of bleeding time is determined on the treated and control wistar rats.

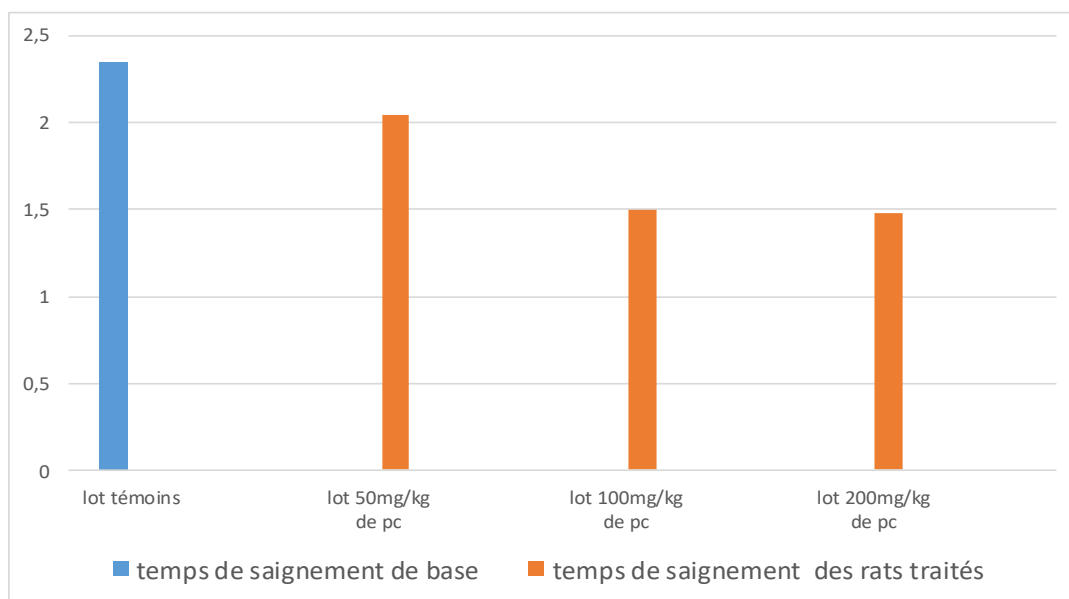


Figure 3 Graphical analysis of the rate of change of bleeding time in control and *F. umbellata* ethyl extract treated rats.

A baseline bleeding time is measured on all rats before treatment, and then after the treatment period, another bleeding time measurement is performed on the treated rats. It is important to note that the bleeding time decreases progressively with the dose to reach a plateau, in comparison with the control, the 100mg/kg dose presents the significant result

Platelet count determination

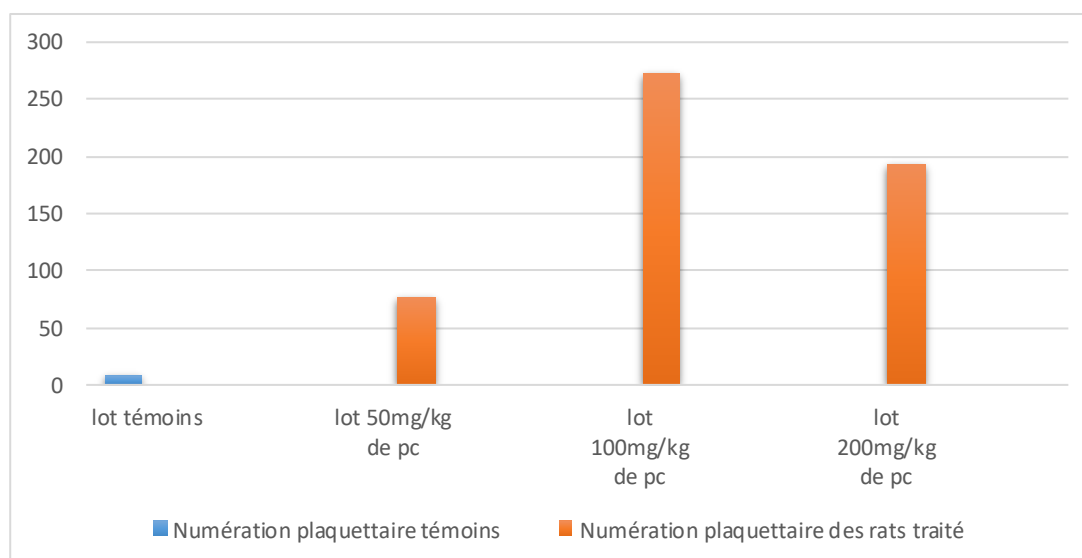


Figure 4 Graphical analysis of the rate of Change in platelet count in normal and *F. umbellata* ethyl extract treated rats.

We note from this graph an increase in the number of platelets between control rats and those treated with *F. umbellata* extract. However, a strong increase in the number of platelets is recorded with the 100 mg/kg dose

Determination of Prothrombin Rate, Peptide and INR

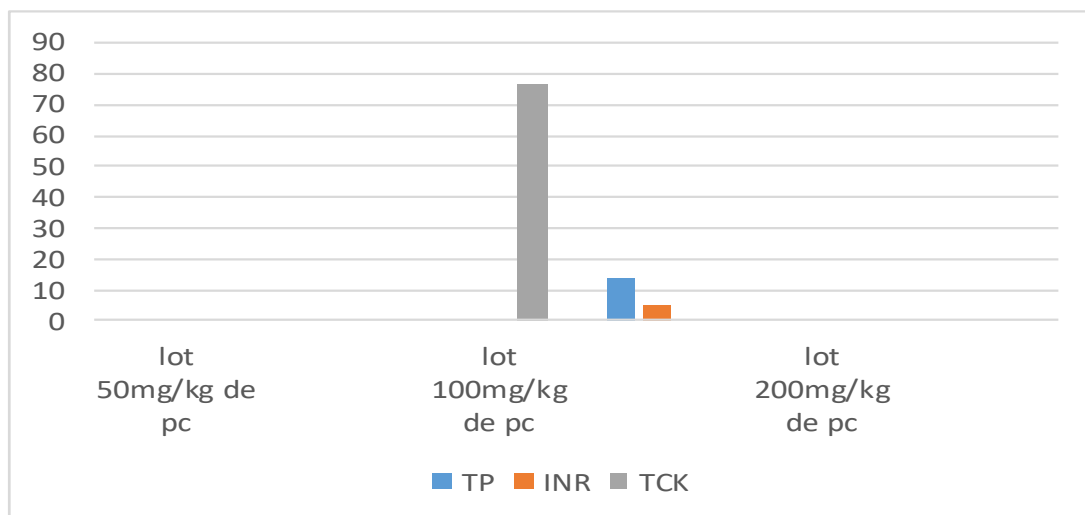


Figure 5 Graphical analysis of prothrombin levels in normal rats and rats treated with ethanolic extract of *F. umbellata*

The graph in figure 23 showing the graphical analysis of the Variation in prothrombin rate, INR and TCK of normal rats and rats treated with ethanolic extract of *F. umbellata*,

allows us to deduce that only the 100 mg/kg body weight dose presents significant data (data are incorporated in the graph)

IV DISCUSSION

According to the results of our study, the ethyl extract of *F. Umbellata* leaves gives a yield of 2.14%. This yield differs from that of Bello K. (2017) and is explained by the fact that the species used for extraction is different.

Chemical study of *Ficus umbellata* shows the presence of flavonosides, heterosides and tannins, Diop D., 2006; similarly Kevin Kamba et al, 2017, there is a low presence of alkaloids in the aqueous extracts of *F. umbellata*. However the methanolic extract of *F. umbellata* was found to contain more flavonoids, flavonols and alkaloids than the aqueous extract.

The first interpretation is shown in figure 11, which shows the effect of the extract on the weight of the rats. The weight of the control rats and those treated with the ethyl extract of *ficus umbellata* leaves for 07 days. We observed an increase in weight in control rats while the weight of rats treated with 50, 100 and 200 mg/kg bw decreased. These results are comparable to those of Bello K (2017), who showed that *Tridax procumbens* extracts slightly reduced or prevented weight gain in rats. This may be due to the lipid-lowering effect thus inhibiting fat accumulation in adipose tissue.

The results obtained on the measurement of bleeding time in wistar rats allow us to note that the bleeding time in the control rat is 2.35 min while the bleeding time after treatment with the extract is 2.05 min at the dose of 50 mg/kg PC and 1.50 min at the dose of 100 mg/kg PC and 1.48 min at the dose of 200mg/kg pc. Thus, the extract significantly reduces the bleeding time with a difference of 85% between the control and the rat treated with the 100mg/kg PC dose. These results are comparable to those of Bello k., 2017 who found that the mean bleeding time without the extract is 2.58 ± 0.31 min and that treated with the extract is 1.61 ± 0.08 . Other research such as Adogo J. L., 2015 shows that the mean bleeding time without the extract is 2.49 ± 0.09 and that treated with the extract is 1.40 ± 0.16 min. The TS is defined by the time between the sectioning of a group of small capillaries and the cessation of the bleeding thus induced. It depends on the quality and quantity of platelets, the thrombogenicity of the vascular wall, two plasma factors (Von Willebrand factor and fibrinogen).

From the analysis of Figure 12, we can deduce that the platelet count was increased. However, in rats treated with ethanolic extract of *Ficus umbellata*, the increase in platelet count is significantly higher in rats treated with 100 mg/kg PC than in those treated with 50 mg/kg PC and those treated with 200mg/kg PC.

Figure 13 provides information on the effect of ethyl extract of *F. Umbellata* on the prothrombin rate and the kaolin partial thromboplastin time. From the analysis of this graph, it appears that only the rats treated with the dose of 100mg/kg bw present a PT = 13.7%, a kaolin cephalin time TCK= 76.9s, and an INR= 5.27. The partial thromboplastin time is measured in seconds and allows the exploration of the endogenous and common pathways of plasma coagulation. It allows the exploration of the coagulation factors involved in these pathways, among which we have factors IX and VIII which are respectively responsible for hemophilia B and A. The prolongation of the patient's TCK greater than 30% of that of the control is significant. The indication of the TCK value allows us to affirm that the ethyl extract of *F. umbellata* acts on these coagulation factors. The measurement of the prothrombin level makes it possible to evaluate the effectiveness of blood coagulation within the body. It explores the extrinsic pathway involving coagulation factors called the prothrombin complex.

In patients on anti-vitamin K, the results are given in the form of INR. The treatment is considered effective when the INR is between 2, 4, and 5, i.e., a prothrombin rate of less than 20%, which is the case for our results. This implies that the intrinsic pathways are ignored. Indeed, the coagulation factors involved in these pathways, namely factors VII, V, X, II, and fibrinogen, are present in minute quantities in the blood, unlike prothrombin which is present in large quantities. It is therefore likely that the extract exerts its pro-coagulant effect by rapid activation of prothrombin. It is not always possible to pass all these tests. In the absence of aPTT, PT, TH, fibrinogen or platelet count, and if the planned procedure or its immediate consequences reveal a real risk of bleeding, at least. To achieve a bleeding time at the earlobe level (Duke), this test can be an interesting alternative to the platelet count. It also provides more general information on primary hemostasis. However, it does not dispense with a study of the coagulation phase in order to reach a coagulation time that will allow a rough quantification of the bleeding disorder without being able to define the cause of the disorder.

CONCLUSION

Hemostasis is the set of mechanisms that ensure the prevention of spontaneous bleeding and the stopping of bleeding by repairing the vascular breach. Hemostasis consists of primary hemostasis leading to platelet thrombus, secondary hemostasis or plasma coagulation which consolidates the platelet thrombus by the constitution of a fibrin network and fibrinolysis, which leads to the enzymatic degradation of the fibrin-platelet mass at the end of the vascular repair. There are many pathologies of hemostasis and they can affect primary hemostasis (platelet abnormalities, central or peripheral acquired thrombocytopenia, constitutional thrombocytopenia, thrombopathies, constitutional or acquired plasma abnormalities) or coagulation (hemophilias, coagulation factor deficiency, etc.). Nevertheless, the treatment of these pathologies is relatively expensive compared to the average standard of living of the Beninese population. Phytotherapy is therefore becoming an alternative for the treatment of these conditions, especially since the African pharmacopoeia in general and Beninese pharmacopoeia in particular is rich in plants with interesting pharmacological properties. The use of plants in the treatment of diseases is a very old practice. In the development of the pharmaceutical industry, medicinal plants still occupy an important place in the therapeutic system.

We had to evaluate the activity of ethanolic extract of *Ficus umbellata* leaves on coagulation. The results showed that the ethanolic extract of *F. umbellata* leaves increases the number of platelets and reduces the bleeding and clotting time. It would be interesting to further research the chemistry, toxicity, therapeutic doses, to better popularize the use of the plant.

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