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Research Article

Phytochemical, toxicity and antihyperglycaemic effects of *Zea mays* Linn leaves' extracts

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Abstract

In the Republic of Benin, several plants, including *Zea mays* Linn *(Z. mays*) are used for the treatment of diabetes without any scientific studies showing their effectiveness. The objective of this study is to investigate the effects of Z. *mays* leaves' extracts on hyperglycaemic rabbits using the Oral Glucose Tolerance Test (OGTT), 2 g/kg of (D) + glucose and on hepatic glucose liberation. Phytochemical screening revealed that the plant leaves contain alkaloids, tannins, mucilage flavonoids, anthocyanin, leuco-anthocyanin, coumarins, heteroside, flavonoid, triterpenoids, steroids, reducing compounds, saponins, oses and holosides. Cytotoxity tests showed that the aqueous and ethanolic extracts were free of toxicity. The extracts have shown anti-hyperglycaemic activities dependent on specific dosage and timing. The effective dose is 500 mg/kg for the aqueous extract and for the ethanolic extract. The extracts are effective as compared with glibenclamide (reference product). Moreover, the *ex vivo* test conducted on the liver revealed that *Z. mays* aqueous extract inhibits the hepatic glucose liberation and 500 mg/kg is the most effective dose.

The results of this study justify the traditional usage of the plant leaves under consideration in the treatment of diabetes.

Key words: *Zea mays* extracts, phytochemical, hyperglycaemia, hepatic glucose, toxicity, Benin.

INTRODUCTION

Diabetes is a metabolic group of diseases characterized by chronic hyperglycaemia (glycaemia ≥ 1. 26 g/L) related to abnormality of carbohydrate, fat and protein metabolism arising from the failure of the body to make and/ or to respond properly to the action of insulin [1]. Diabetes is a serious disease which can cause heart diseases, blindness, kidney diseases, sexual impotence, non-healable wounds and even amputations. These complications make diabetes very serious and decrease diabetic patients' life expectancy. [2]. According to the International Diabetes Federation (IDF), there were about 425 million diabetic people (aged 20 to 79 years) in the world in 2017. IDF assumes the prevalence could reach 629 million by 2045 [3].The strong expansion of the disease and its seriousness require effective and appropriate care. Unfortunately, due to the high cost, inaccessibility and side effects of modern medicine treatment, the majority of the populations in developing countries resort to traditional medicines. According to the World Health Organisation (WHO), traditional medicine is defined as "all knowledge, competencies and practices based on theories, beliefs and experiences of people's own culture, and which they use to prevent, diagnose, relieve or treat most physical and mental ailments" [4].Traditional medicine is a serious alternative or at least a significant and useful complement to the field of modern pharmacy, which uses modern chemistry [5].This means that several plants are used in traditional medicine in Benin to treat diabetes but very few of them have been submitted to a scientific study. It is to correct this situation that the current study is conducted in order to scientifically justify the use of *Z. mays* leaves by the population of the State Department of Oueme (Republic of Benin) for the treatment of diabetes.

MATERIAL AND METHODS

Plant material

The plant material is composed of *Z. mays* leaves, harvested in the state Department of Oueme (Republic of Benin). The plant was identified and certified by the National Herbarium of Benin at the University of Abomey- Calavi where the specimen was deposited and was given the following number: AA 6508/HNB.

Animal material

Albino rabbits (*Oryctolagus cuniculus*) of both sexes were used in this study. Their average weight was 1.5 ± 0.06 kg. They

were housed in the Effort Physiology Research Unit of National Institute of Youth, Physical and Sport Education under standard conditions (light and dark alternated cycle of twelve hours and at room temperature). The animals had free access to water and food.

Albino rabbit liver was used to conduct the experiment on hepatic glucose liberation.

Aqueous and ethanolic extractions

The aqueous extract was made using 50 g of raw powder decoction in 500 mL of boiling distilled water for 30 min and then filtered. The ethanolic extract was made by macerating 50 g of raw powder in 500 mL of ethanol (96%) using a homogenizer for 48 h, then filtered. The product was evaporated using a Rotavapor of trademark STUART/RE 300 then put into the Memmet oven at a temperature of 50 °C to perfect the extracts' drying. Finally, the extracts were conserved at 4 °C in a refrigerator prior to the experiment.

Phytochemical analysis

Phytochemical analysis is based on precipitation reactions and differential colouring of the main chemical compounds in the plant 6.

Larval toxicity of extracts

The experiment was conducted on *Artemia salina* leach (larvae brine shrimps) harvested from the incubation of shrimp eggs in sea water [7].

Anti-hyperglycaemic activities of *Z. mays* extracts

The experimental model used was that of glucose overloading [8-11]. It consisted of administering orally to rabbits two grams per kg of body weight (2 g/kg) of (D) + glucose diluted in seven millilitres of distilled water after a prior fasting for eighteen (18) hours before the force feeding. To conduct the experiment, forty (40) rabbits were divided into eight (8) groups of five (5) rabbits each (2 females and 3 males)

- **Group 1:** control group in the hyperglycaemic condition caused by oral-doses of glucose with 2 g/kg body weight

(D) + glucose in 7 mL of distilled water.

- **Group 2:** standard experiment group received 10 mg per kg of body weight of glibenclamide two (2) hours before the OGTT.

- **Group 3, 4 and 5:** received oral-doses of 500 mg/kg, 1000 mg/kg and 1500 mg/kg body weight of aqueous extracts of *z. mays* (ZMA) respectively.

- **Group 6, 7 and 8**: received oral-doses of 500 mg/kg, 1000 mg/kg, and 1500 mg/kg body weight of the ethanolic extracts of *Z. mays* (ZME) respectively.

The glycaemia was observed for five (5) hours. Glucose level was measured just after the force feeding (t = 0), and at 30, 60, 120, 180, 240, and 300 min after the OGTT.

A SD CHECK GOLD Blood glucose monitoring system glucometer (Standard Diagnostics, Inc. Korea) was used for the measurement. Blood samples were collected by puncture from the marginal vein of the rabbit's left ear.

Hepatic glucose liberation test

The washed liver method of Claude Bernard (1955), implemented and improved by other researchers, was used [12-14]. As a matter of fact, an anaesthetic Wistar rat was sacrificed and after opening the abdominal cavity by making an incision, its liver was immediately harvested, weighted and put into a flask containing Mac Ewen physiologic solution. The liver was then cut into pieces that averaged 300 mg, and washed in the Mac Ewen solution again. The pieces were divided into different solutions:

- Solution A: (control solution): 1 mL of Mac Ewen solution;

- Solution B: (reference) 1 mL Mac Ewen solution + 2.5 UI/mL insulin solution to 100 UI/mL;

- Solution C: 1 mL Mac Ewen solution + 62.5 mL of aqueous extract (ZMA 62.5 mg/mL)

- Solution D: 1 mL Mac Ewen solution + 125 mg/mL of aqueous extract (ZMA 125 mg/mL)

- Solution E: 1 mL Mac Ewen solution + 250 mg/mL of aqueous extract (ZMA 250 mg/mL)

- Solution F: 1 mL Mac Ewen solution + 500 mg/mL of aqueous extract (ZMA 500 mg/mL)

All the solutions were incubated in Bain-Marie Thermostat 37 °C throughout the experiment. After 20 min of incubation, the glucose level was measured by enzymatic method based on the oxidation of glucose at 500 nm for each time t = 0, 10, 20, 30, 40, 50 and 60 min with spectrophotometer Biomate Thermo Spectonic Genesys 6 (Rochester NY USA). The glucose concentration for the sample was calculated using the following formula:

Glucose concentration = (DO sample/DO glucose standard) x 1 g/L; DO = optical Density.

The experimental protocols have been approved by Benin Institute of Applied Biomedical Science Ethical Committee.

Statistical analysis

Data from the experiments are presented as mean ± standard error of the mean (X ± SEM). The statistical analysis of results was conducted using the STATISTICA software 5.5 STAT Soft Inc. A statistical analysis of mean was conducted following One-Way ANOVA "t- tests for paired samples" and " t-tests for independent samples." A level of $p < 0.05$ was considered significant.

RESULTS

Extraction yield was 5.68 and 11.56% respectively for the ethanolic and aqueous extracts.

Phytochemical analysis

Phytochemical analysis of raw powder of Z. mays showed the presence of various chemical compounds as presented in the following table I.

Table I: Results of phytochemical screening

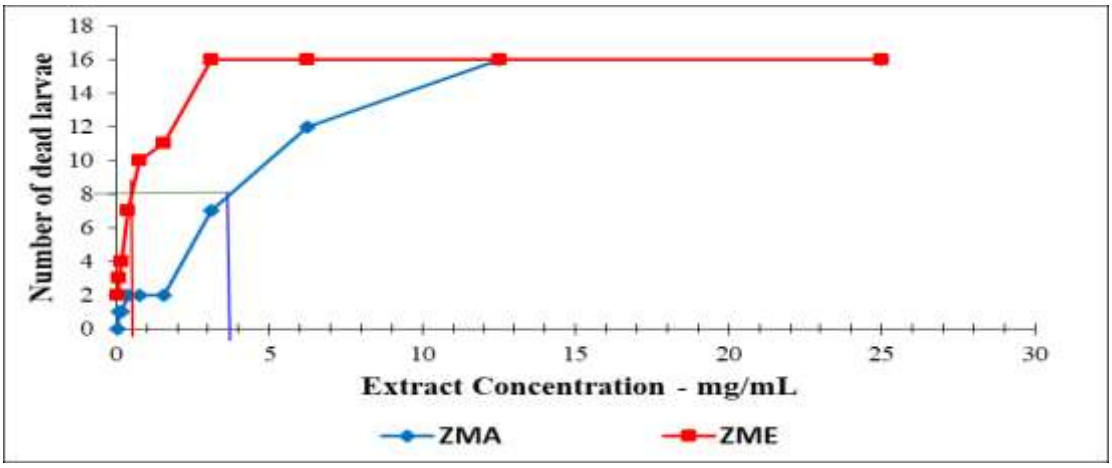
Chemical compounds	Results
Alkaloïds	+
Catechetical Tannins	+
Gallic Tannins	+
Flavonoids	+
Anthocyanin	+
Leuco-Anthocyanin	+
Saponosids	+
Steroids	+
Triterpenoids	+
Quinonics compounds	-
Cyanogenics compounds	-
Mucilage	+
Coumarins	+
Reducing compounds	+
Oses and Holosides	+
Heteroside Cardiotonics	-
Cardenolids	-
Free Anthracenes	-
Combined Anthracenes (C-Heterosids)	-
Combined Anthracenes (O-Heterosids)	-
Narcotics	-
Opium	-
Water content	10.50 %

- Absent, + present

Larval toxicity of Zea mays aqueous and ethanolic extracts

Results of the toxicity test of *Z. mays* aqueous and ethanolic extracts conducted using *Artemia salina* are shown in figure 1

A toxicity test conducted using *Artemia salina larvae* showed the lethal concentration (LC_{50}) at which half of larvae died for each extract. This concentration (LC_{50}) for aqueous extract is 3.75 mg/mL and 0.5 mg/ml for ethanolic extract.



ZMA: Z. mays aqueous extracts; ZME: Z. mays ethanolic Extract; LC_{50}: lethal concentration of half of the larvae

Figure 1: Larval mortality variation based on the concentration of *Z. mays* aqueous and ethanolic extracts (N = 3), LC50 (mg/mL): ZMA = 3.75; ZME = 0.5

Anti-hyperglycaemic activities of *Zea mays* extracts on Oral Glucose Tolerance Test (OGTT)

The changes caused by OGTT and the effects of various extracts over a five hour bloc are shown in figures 2 and 3.

Oral administration of glucose to the control group of rabbits caused a significant increase of glucose level on the 60th min as compared to the initial data (1.61 ± 0.05 compared with 0.90 ± 0.02 g/L; p = 0.004). From the 120th min, the glucose level decreased significantly (1.28 g/L, p = 0.005) as compared to that of the 60th min. This decrease remained consistent up to the 300th min (p = 0.004) (figures 2 and 3).

The group of rabbits to which we administered glibenclamide reached its highest level of glucose on the 30th min with 1.53 g/L ± 0.04 (p = 0.00003). Compared with the control group, anti-hyperglycaemic effect started on the 60th min and reached its highest level on the 120th min (0.98 g/L, p = 0.0007). The decrease continued gradually up to the 300th min (0.78 g/L; p = 0.02) (figures 2 and 3).

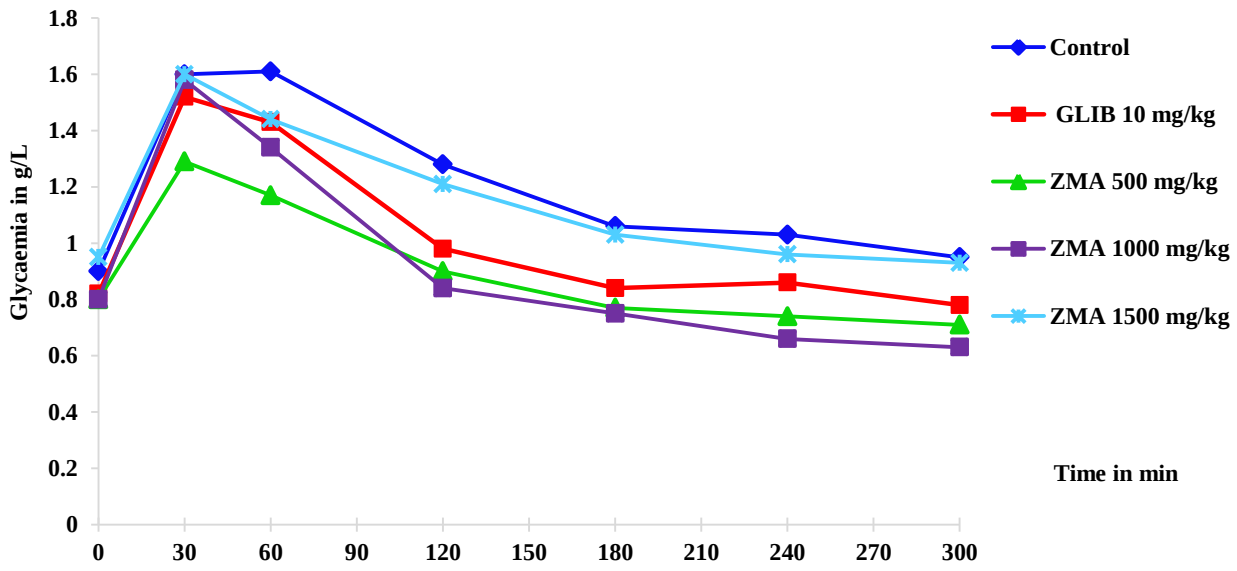


Figure 2: Effect of *Zea mays* aqueous extract on glycaemia evolution, N = 5 per group, data are presented as mean ± standard error of the mean (X ± SEM). P < 0.05 as compared to the control group (ANOVA).

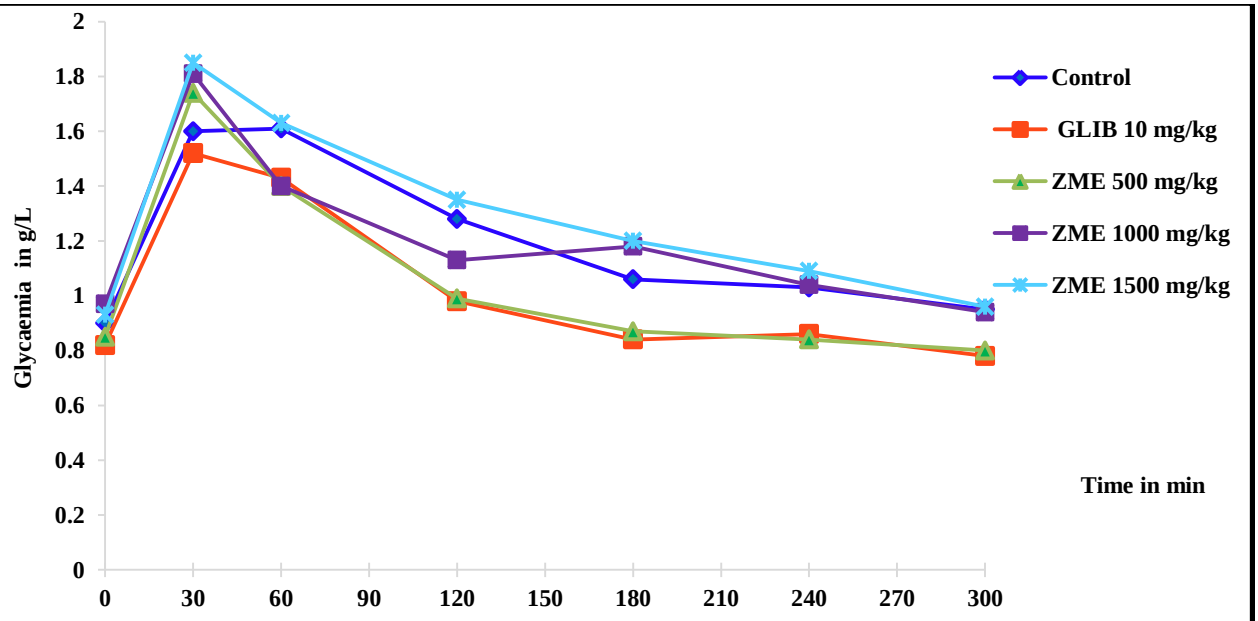


Figure 3: Effect of *Zea mays* ethanolic extract on glycaemia evolution, N = 5 per group, data are presented as mean ± standard error of the mean (X ± SEM). P < 0.05 as compared to the control group (ANOVA).

For all the groups of rabbits for which *Z. mays* aqueous extract was used, the highest level of hyperglycaemia was reached on the 30th minute. Anti- hyperglycaemic effects were observed from the 60th minute to the 300th minute. Significant differences were observed between averages of glycaemia for doses 500 and 1500 mg/kg from the 120th minutes to the 300th minutes (0.71 g/L compared to 0.93 g/L for p = 0.001) on one hand, then 1000 and 1500 mg/kg (0.63 g/L compared to 0.93 g/L; p = 0.000008) on the other hand. However, there was no significant difference between doses 500 and 1000 mg/kg. It appears that the lowest effective dose is 500 mg/kg for *Z. may* aqueous extract. Its effect is higher than that of glibenclamide throughout the experimentation. (figure 2).

As far as the groups for which ethanolic extract was used are concerned, the highest level of glycaemia was reached on the 30th minute after **OGTT.** Anti-hyperglycaemic effects were observed from the 60th min to the 300th min. Anti-hyperglycaemic effects of the 500 mg/kg dose compared to the others revealed significant differences from the 120th min to 300th min (0.80 g/L compared to 0.94 g/L for 1000 mg/kg; with p = 0.01; 0.80 g/L compared to 0. 96 g/L for 1500 mg/kg with p = 0.0007). It transpires from all this that the lowest effective dose is 500 mg/kg for *Z. may* ethanolic extract. Its effect is the same as that of glibenclamide from the 60th min to the 300th min (figure 3). Moreover, the comparison of the anti-hyperglycaemic effect of aqueous extract to the dose of 500 mg/kg and the ethanolic extract dose of 500 mg/kg revealed significant differences between averages of glycaemia on the 60th min (1.17 g/L compared to 1.40 g/L; p = 0.007) and on the 120th min (0.90 g/L compared to 0.99 g/L; p = 0.04); the dose of 500 mg/kg of aqueous extract was more effective. Consequently, the highest effective dose is 500 mg/kg for the aqueous extract.

The effect of *Zea mays* aqueous extract on glucose hepatic liberation

Average values of the liberated glucose in extract solutions of different concentrations of *Z. mays* are presented below in the concentration-time curves (figure 4).

All of the concentrations inhibited the hepatic glucose liberation. The inhibition rates as compared to the control solution vary from 2.47 to 19.26%. The highest rate was observed on the 50th min after the incubation with the dose of 500 mg/kg per body weight. As compared to the control solution, there was no significant inhibition. *Z. mays* aqueous extract appears to have a weak inhibitory effect on glucose hepatic liberation.

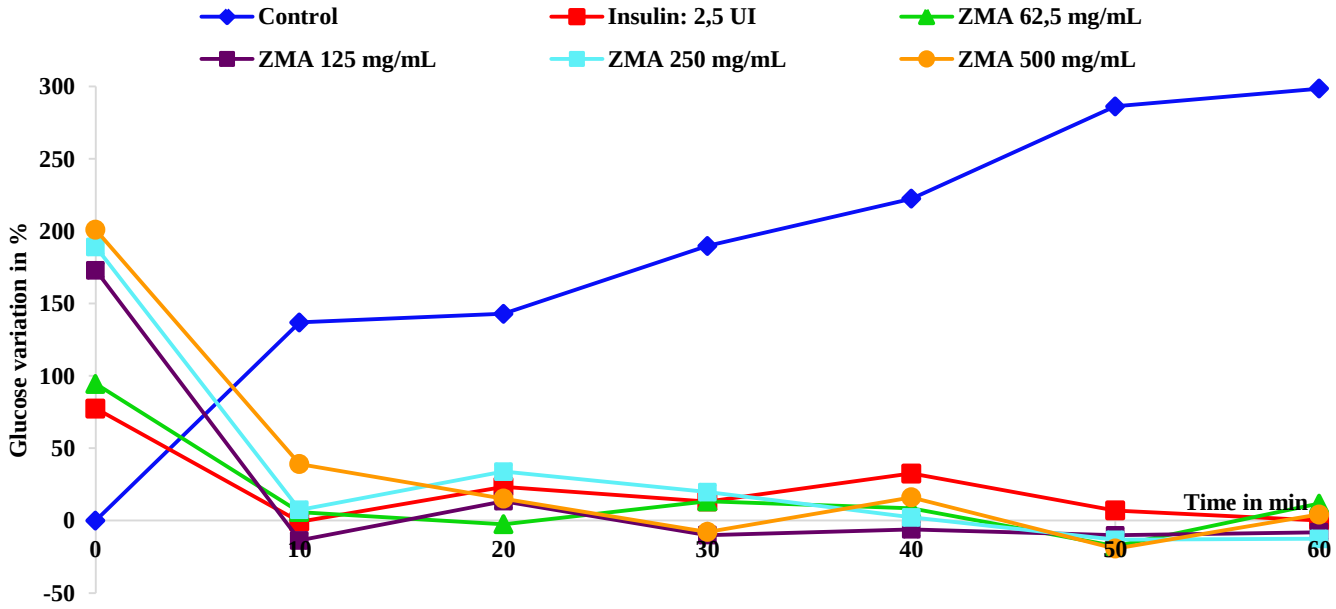


Figure 4: the effect of *Zea. mays* aqueous extract on the hepatic glucose liberation (mean of triplicate).

DISCUSSION

Scientific studies based on analytical methods and new experiments enable the researchers in the medical field to discover more and more the importance of empirical prescriptions of medicinal plants [15]. The objective of this study was to investigate the effects of *Z. mays* extracts administered orally on hyperglycaemic rabbits (HGPO), and glucose hepatic liberation. The research results show that *Z. mays* leaf aqueous extracts yield better results than ethanolic extract. Water was shown to extract more chemical compounds than ethanol. Phytochemical analysis revealed several chemical compounds in the raw powder of *Z. mays* leaves: alkaloids, tannins, flavonoids, anthocyanin, leuco-anthocyanin, saponosids, steroids, triterpenoids, mucilages, coumarins, reducing compounds, oses and holosides. In fact, alkaloids have sympatholytic actions on the autonomous nervous system; a central nervous system stimulant etc. [16]. They also cause anti-hyperglycaemic activity by alpha-glucosidase inhibitor [17]. Other studies also showed that flavonoids, tannins and coumarins promote anti-hyperglycaemic activity [18; 19]. Anti-edematous effects, antioxidants, anti-inflammatory properties of flavonoids, saponosids, steroids and triterpenoids can prevent or correct complications caused by diabetes such as diabetic retinopathy and diabetic foot. Moreover, these complications can be prevented or corrected by the

accelerating action of the regenerative visual crimson of anthocyanin and leuco- anthocyanin, and then by tannin's antiseptic and antibacterial action in the cases of skin ulceration [16]. *Z. mays* is rich in mucilage, often needed for its healing and intravenous properties. [20]. Taking into account the biological properties of *Z. mays* chemical compounds, it is quite clear that the plant is recommended for the treatment of hyperglycemia and to prevent or treat some chronic complications of diabetes such as oxidative stress, inflammation, skin diseases, diabetic foot etc.

Human cells, specifically those of colon carcinoma (HT-9), lung carcinoma (A-549) and human carcinoma nasophrygian (9PS and 9kB) are similar to the *Artemia salina* [21]. It appears that any toxic effect occurring on those larvae could also occur on human cells. The results of the larvae toxicity test showed that all LC_{50} values are higher than 0.1 mg/mL, the value above which the extract is not toxic [22]. We can say subject to other findings of the toxicity tests that *Z. mays* aqueous and ethanolic extracts are not cytotoxic and can be consumed in decoction and maceration. This accounts for the way the population uses this plant.

With diabetic subjects, treating hyperglycemia as quickly as possible is necessary in order to delay or avoid complications. The results of the Oral Glucose Tolerance Test (OGTT) showed that the bodies of non- treated rabbits (control group with hyperglycaemia) naturally absorb the glucose overload. It appears that the body is able to transform any food glucose excess and put it aside for later use. Our results are similar to those of other studies conducted on other plants with different types of animals. [8-10, 14, 23].

Administering a single dose of 10 mg/kg of body weight of glibenclamide, two hours before OGTT, has not only reduced the peak blood glucose as compared to the control group but it has also caused an early decline of OGTT. These results are also similar to those of several other researchers [8-10, 23].

As far as the *Z. mays* extracts are concerned, the results showed that the minimum effective dose is 500 mg/kg for the two extracts, aqueous and ethanolic. The extract anti-hyperglycaemic effect at 500 mg/kg is comparable to glibenclamide action at 10 mg/kg and the *Z. mays* aqueous solution is the most effective.

The aqueous extract effectiveness could be justified by the capacity of water to extract chemical compounds causing this anti- hyperglycemic activity. This accounts for the better yield obtained for aqueous extract. In fact, most of the chemical groups of these plants are water soluble, and could be causing the observed activities; this fact justifies the way these plants are used by tradipractitioners [9, 24]. Moreover, the low observed activity of ethanolic extract could be justified by the lipophilic property of the solvent (ethanol). This solvent withdraws fats and lipids from plants. These results are in accordance with those of other researchers who observed a low anti- hyperglycemic activity with hydro-ethanolic extract of leave mixture- bark of *Casuarina equisetifolia* (Filao) as compared with aqueous extract. As a whole, anti- glycemic effects observed in this study are similar to those obtained with other plants containing most of the active ingredients in the leaves of Z. *mays* [8, 10, 23]. It appears that the anti-hyperglycemic activity caused by the leaves of Z. *mays* is due to the effect of its active biological compounds. Studies conducted on purple maize seeds showed that they are rich in anthocyanin and functional phenolic compounds which reduce high blood pressure, diabetes and cancer effects rather than having other potential medical use [25]. Purple maize anthocyanin stimulates insulin secretion through pancreas Islet cells with no adverse, but rather protective effects [26, 27]. In fact, phytochemical analysis reveals that the leaves of Z. *mays* contain phenolic compounds, anthocyanin, etc. So the plant leaves are rightly recommended for the treatment of diabetes and its complications.

The results of the hepatic glucose test showed that the liver pieces of the control group rats (pieces of liver incubated in Mac Ewen solution) release glucose continuously and differ based on duration. This confirms that the liver is capable of storing glucose in the form of glycogen during postprandial time and releases it when there is deficiency. All doses (62.5; 125; 250 and 500 mg/mL) inhibit hepatic glucose liberation for the experimental groups as compared to the control group and to insulin (reference). This inhibition could be caused by a decrease or blockage of one of the enzymes (phosphorylase glycogen, phospho-glucomutase and glucose-6-phosphatase) responsible for liver glycogenolysis. Our results are similar to those of other studies [12, 14, 28]. It is shown that *Eleais guineensis Jacq (arecaceae*) flavonoid extract (9.76 mg/mL) inhibits hepatic glucose liberation significantly at 135.45% as compared to the control group [28]. Therefore, the observed hepatic glucose inhibition could be caused by individual or combined action of the extract chemical compounds. It is worth mentioning that plants have a variety of action mechanisms.

CONCLUSION

The results obtained within the framework of this study showed that leaves of *Z. mays* contain many chemical compounds capable of conferring therapeutic properties. Moreover, *Z. mays* leaf aqueous and ethanolic extracts can be consumed without risk of intoxication. *Z. mays* extracts, when consumed at dose of 500 mg/kg of body weight, cause anti-hyperglycaemic activity comparable to and even more effective than glibenclamide action (reference product). The extracts also inhibit hepatic glucose liberation. All in all, these results enable us to say that Z. *mays* is a promising plant in diabetes management. All of these favorable results support the traditional medicinal usage of *Z. mays* leaf, precisely for diabetes treatment. However, future studies are necessary to further elucidate therapeutic properties and clinically validate *Z. mays* leaf extracts.

Conflict of interests

The authors have not declared any conflict of interests

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