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Hypoglycemic and antihyperglycemic activities of the aqueous ethanolic extracts of *Gymnema sylvestre* (RETZ) R. Br. Ex SCHULT and *Sclerocarya birrea* (A RICH) HOCHST

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Gymnema sylvestre (Retz.) R. Br. ex Schult (Asclepiadaceae) and _Sclerocarya birrea_ (A. Rich) Hochst (Anacardiaceae) are two plants used in Burkina Faso in traditional medicine and in the form of phytomedicine in the treatment of diabetes. This study evaluated the effect of aqueous ethanolic extracts of leaves of _Gymnema sylvestre_ and _Sclerocarya birrea_ on glycemia. A phytochemical screening of the extracts obtained by successive exhaustion after maceration of the leaves was carried out. The effect of these extracts was tested on basal plasma glucose and oral tolerance glucose in mice. Saponosides, tannins, flavonoids, sterol and triterpene glycosides, reducing compounds and coumarinic derivatives were found in the leaves of both plants. Alkaloids were also detected in the leaves of _G. sylvestre_ and anthocyanosides in the leaves of _S. birrea_. The aqueous ethanolic extracts from leaves of _G. sylvestre_, _S. birrea_ or both in combination at 100 mg/kg body per weight did not have a significant hypoglycemic effect on basal plasma glucose but significantly reduced ($p<0.05$; $p<0.001$) peak of hyperglycemia. The effect of the combination of the aqueous ethanolic extracts of the two plants on hyperglycemia is greater (47% reduction) than the effect of the aqueous ethanolic extracts of _G. sylvestre_ (21% reduction) or _S. birrea_ (36% reduction) alone. These results show that the combined use of _G. sylvestre_ and _S. birrea_ aqueous ethanolic extracts would be an asset in the treatment of diabetes.

Key words: *Gymnema sylvestre*, *Sclerocarya birrea*, oral glucose tolerance test, hypoglycemia, Antihyperglycemia.

INTRODUCTION

Diabetes is a serious, long-term condition that occurs when the body cannot produce any or enough insulin or

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cannot effectively use the insulin it produces (IDF, 2019). According to WHO estimates, 422 million people worldwide are diabetic and 1.6 million deaths were directly caused by diabetes in 2016. Over 80% of diabetes deaths occur in low- and middle-income countries. Diabetes could become the 7th leading cause of death worldwide by 2030 (WHO, 2020). The increase in the number of deaths is due to a rich diet, obesity and sedentary population. Diabetes is a complex disease both in its physiopathological mechanisms and in the genesis of its complications.

The pathophysiology of type 2 diabetes mellitus reveals that oxidative stress is one of the factors that plays a role in the pathogenesis of insulin resistance, impaired insulin secretion, glucose utilization, impaired hepatic glucose metabolism coupled with activation of inflammation pro-inflammation cytokines, culminating in type 2 diabetes (Rehman and Akash, 2017). Type 2 diabetes requires medication and hygieno-dietetic treatment. The high cost of conventional drugs encourages patients to use traditional drugs. Beyond economic reason, this recourse is primarily cultural. Indeed, the traditional pharmacopoeia is rich in traditional recipes based on medicinal plants for the management of many pathologies. In Africa, over 80% of the population depends on medicinal plants for the treatment of various diseases (WHO, 2004). This traditional medicine based on medicinal plants is a hope for populations but also for researchers who see it as a source of new molecules for therapeutics.

Many researchers have embarked on the exploitation of traditional medicine through the scientific study of the medicinal plants used. Recovery requires the standardization of extracts, as well as the evaluation of their safety and efficacy. The final step is the development of phytomedicines. Many plants are traditionally used for the treatment of diabetes, including *G. sylvestre* (Retz.) R. Br. ex Schult (Asclepiadaceae) and *S. birrea* (A. Rich) Hochst (Anacardiaceae). *G. sylvestre* is a liana native to Africa and Asia. Also called “miracle fruit”, this plant is used in the treatment of several diseases including diabetes. In India its leaves have been used for their hypoglycemic effects for more than two millennia (Kumarmall et al., 2009). *S. birrea* or “African plum” is an important alimentary, commercial, cultural and ethnomedicinal plant in Africa. The tree is commonly found in semi-arid, deciduous and savannah regions of sub-Saharan Africa (Borochov-Neori et al., 2008). Pharmacological studies conducted by several groups of researchers have shown that *S. birrea* has antidiarrheic, anti-diabetic, anti-inflammatory, antibacterial, antiplasmodial, anti-hypertensive, anticonvulsant, antifungal, and antioxidant activities (Ojewole et al., 2010). *G. sylvestre* has anti-diabetic, antimicrobial, anti-obesity and anti-inflammatory properties (Saneja et al., 2010).

In Burkina Faso, these two plants are used by tradipraticians for the treatment of diabetes (Nacoulma, 1996; Youl et al., 2013). Formulations in the form of capsules based on raw powders from the dry leaves of *G. sylvestre* (Gymnefla) and *Sclerocarya* birrea (Diabefla) are made by the Phytofla laboratories.

The aim of this study was to assess the effect of aqueous ethanolic extracts of leaves of *G. sylvestre* and *S. birrea* on plasma glucose.

MATERIALS AND METHODS

Chemicals

Quercetin, rutoside and tannic acid were purchased from Merck (Germany). Metformin (Glucophage 500 mg) was obtained from Merck (Switzerland). Glucose, chloroform and methanol were purchased from Prolabo (France). Ethanol was obtained from Scharlab (Spain). Ammoniac was purchased from Sigma-Aldrich (St. Louis, MO, USA). Ferric chloride (FeCl3) was obtained from Labosi (France). Ascorbic acid was purchased from Fluka (England). All the chemicals used in the study were of analytical grade.

Plant material and sample extraction

G. sylvestre and *S. birrea* leaves were collected in Sideradougou for the first and Tangora for the second, in the west of Burkina Faso, and were authenticated by Phytofla Laboratories.

The collected leaves were air-dried and ground into a fine powder in a mill. About 240 g of the powdered leaves of each plant were extracted with 1200 mL of ethanol/water (80:20) by maceration for 48 h under constant shaking at 25°C. The solution was filtered 2 times through cotton wool and centrifuged at 3000 rpm for 10 min. The extract was collected and concentrated in a rotatory evaporator (Büchi R-205, Flawil, Switzerland) at 50°C under reduced pressure. The concentrated extracts were then oven-dried (50°C) for 72 h before being used for the study. The oven-dried extracts were resolubilized for phytochemicals screening and for pharmacological experiments.

Phytochemical screening of extracts

A successive exhaustion with a test sample of the dry residue of the aqueous-ethanolic extract yielded 3 crude extracts: A chloroformic extract (CE), an aqueous-methanolic extract (AME) and an aqueous extract (AE). The extracts were qualitatively assayed for the presence of phytochemicals such as sterolic and triterpenic glycosides, flavonoids, saponosides, anthocyanosides, anthracenosides, tannins, reducing compounds, oses, and holosides according to the method of Ciulei (1982) and by thin-layer chromatography.

Animals

Healthy adult male Naval Medical Research Institute (NMRI) mice weighing between 30 and 40 g, purchased from International Research and Development Centre for Subhumid Livestock Farming (Bobo-Dioulasso, Burkina Faso) were used in the study. Mice were acclimated for at least 15 days before the experiment was started. The animals were kept under standard laboratory conditions (12 h light: 12 h dark and 25±3°C). They were fed standard commercial laboratory chow enriched to 29% protein (granules form). They had *ad libitum* access to food and water. All experiments were conducted in accordance with international standards of animal welfare as recommended by the European

Union on Animal Care (CCE Concil 86/609).

Pharmacological experiment

Experimental design

The choice of the dosages was based on the literature data related to *G. sylvestre* and *S. birrea* toxicity (Ojewole[b], 2003a; Gurav et al., 2007) and usual doses used by Phytofla (21 mg/kg body weight/day) for assessing biological activities of plants. A high dose of 100 mg/kg body weight was selected for the study of basal plasma glucose.

Effect of extracts of plants on basal plasma glucose: For the test of the effect of extracts on basal plasma glucose, the mice were divided into five equal groups, each including six animals:

1. Control group (n=6): Mice received by gavage 0.5% aqueous-ethanol (10 mL / kg body per weight)
2. Reference (Metformin) group (n=6): Mice received by gavage metformin 500 mg / kg body weight.
3. G. sylvestre group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* 100 mg/ kg body weight
4. *S. birrea* group (n=6): Mice received by gavage aqueous ethanolic extract of *S. birrea* 100 mg / kg body weight
5. G. sylvestre + S. birrea group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* associated with *S. birrea* 100 mg / kg body weight (50:50 v/v).

Prior to administration of treatments by orale route, mice were fasted for 14 h and their basal plasma glucose was determined. The glycemia was then determined at the tail of the animal by using a glucometer every hour for three hours.

Effect of extracts of plants on glucose tolerance: For the test of the effect of extracts on oral glucose tolerance, the mice were divided into eleven equal groups, each including six animals:

1. Control group (n=6): Mice received by gavage 0.5% aqueous-ethanol (10 mL / kg body weight)
2. Reference (Metformin) group (n=6): Mice received by gavage metformin 500 mg / kg body weight.
3. *G. sylvestre* group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* 12.5 mg/kg body weight.
4. *G. sylvestre* group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* 25 mg/kg body weight.
5. *G. sylvestre* group (n=6): Mice received by gavage aqueous ethanolic extract of *G.sylvestre* 100 mg/kg body weight.
6. *S. birrea* group (n=6): Mice received by gavage aqueous ethanolic extract of *S. birrea* 12.5 mg/kg body weight.
7. *S. birrea* group (n=6): Mice received by gavage aqueous ethanolic extract of *S. birrea* 25 mg/kg body weight.
8. *S. birrea* group (n=6): Mice received by gavage aqueous ethanolic extract of *S. birrea* 100 mg/kg body weight.
9. G. sylvestre + S. birrea group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* associated with *S. birrea* 12.5 mg/kg body weight (50:50 v/v).
10. G. sylvestre + S. birrea group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* associated with *S. birrea* 25 mg/kg body weight (50:50 v/v).
11. G. sylvestre + S. birrea group (n=6): Mice received by gavage aqueous ethanolic extract of *G. sylvestre* associated with *S. birrea* 100 mg/kg body weight (50:50 v/v).

The procedure consists of administering to animals by gavage, glucose 20% (10 mL/kg) after a 14-hours fasting. Ninety minutes before glucose loading, the basal plasma glucose was determined, then vehicle, extracts or metformin who was used as a reference drug were administered by gavage. At the time $t_{0,}$ corresponding to the time of glucose administration, blood glucose level we measured and then caused glucose loading. Blood samples were obtained from tail vein of the mice, then glycemia was measured every thirty minutes for two hours using a glucometer by the glucose oxidase method.

Statistical analysis

The results were expressed as mean ± standard error on average (sem). The data were processed and analyzed using Microsoft Office Excel 2007 and Prism® version 5.03 software. This software made it possible to check the homogeneity of the weights of the animals, to evaluate the average glycemia at different times. The ANOVA test with Bonferroni correction was used for the comparison of means. A value of $p<0.05$ was set as the significance threshold. For the calculation of the percentage reduction of basal plasma glucose, the formula used was:

$$\% \text{ change} = \frac{Gt-Go}{Go} \times 100$$

Go: Glycemia at time t_o; Gt: Glycemia at time t.

The percentage of reduction of the peak of hyperglycemia at the 30th minute (t_{30}) was determined by using the following formula:

$$\% \text{ reduction} = \frac{Gt-GT}{Gt} \times 100$$

Gt: Mean glycemia of the control group. GT: Mean glycemia of treated groups.

RESULTS AND DISCUSSION

Phytochemical screening of *G. sylvestre* and *S. birrea* leaves

The chemical groups revealed in the extracts of the two plants by thin-layer chromatography were steroidal and triterpenic glycosides in chloroformic extracts, flavonoids, saponosides and tannins in aqueous-methanolic extracts. Anthocyanosides were found in addition in *S. birrea* aqueous-methanolic extract and anthracenosides in *G. sylvestre*.

The phytochemical results showed that the aqueous-methanolic extract of *G. sylvestre* leaves would contain alkaloids, tannins, anthracenosides, flavonoids, sterol and triterpene glycosides and saponosides. The aqueous extract would contain saponosides and tannins in trace state. Our results are in agreement with those of several authors (Farzana and Muhammad, 2010; Gopinath et al., 2012; Ahirwal et al., 2013; Patel, 2017).

As in *G. sylvestre*, the aqueous-methanolic extract of the leaves of *S. birrea* would also contain tannins, flavonoids, saponosides, sterol and triterpenic glycosides, and anthocyanins. The aqueous extract would contain tannins and traces of saponosides. Unlike *G. sylvestre,* this study showed the presence of anthocyanosides in the leaves of *S. birrea*. Dagnoko also reported in 2009 the presence of gallic tannin in *S. birrea* leaves, but no

Table 1. Effect of aqueous ethanolic extracts of *G. sylvestre* and *S. birrea* leaves on basal plasma glucose.

Groups	Treatments	Basal plasma glucose					
		Baseline (h)	Time following administration of treatments (hour)			Maximal reduction	Percentage of reduction
		0	1	2	3		
		(mmol/L)					
Control	Vehicle	5.50 ± 0.54	5.81 ± 0.44	5.91 ± 0.52	5.50 ± 0.47	0	0
Metformin	500 mg/kg	5.85 ± 0.59	5.35 ± 0.38	4.65 ± 0.15	4.26 ± 0.20**	1.59	27.17
GS	100 mg/kg	5.28 ± 0.15	5.56 ± 0.46	5.18 ± 0.65	4.88 ± 0.59	0.40	7.57
SB	100 mg/kg	5.51 ± 0.41	6.60 ± 0.56	6.36 ± 0.32	5.48 ± 0.57	0.03	0.54
GS+SB	100 mg/kg	6.13 ± 0.49	5.95 ± 0.51	5.56 ± 0.33	5.03 ± 0.72	1.10	17.94

Values are means ± sem (n=6 animals). **p<0.01 significant different from control group. GS = *Gymnema sylvestre*; SB = *Sclerocarya birrea;* Vehicle =0.5% aqueous-ethanol.

anthocyanosides (Dagnoko, 2009). This difference in results could be explained by the influence of ecological, edaphic or climatic conditions on the quantitative and qualitative composition of plants in secondary metabolites. A recent study showed that methanol extracts of the leaves of *S. birrea* is rich in flavonoids (132.7 ± 10.4 mg of quercetin equivalents/g) (Russo et al., 2018).

Pharmacological study

Considering the results of phytochemistry, the study opted to use the aqueous ethanolic extract to carry out the pharmacological study. No death or remarkable signs of external toxicity were observed in the groups of mice that were given aqueous ethanolic extract of *G. sylvestre* and *S. birrea* leaves.

Effect of aqueous ethanolic extracts of *G. sylvestre* and *S. birrea* leaves on basal plasma glucose

The test in normoglycemic animals made it possible to investigate a hypoglycemic effect of the aqueous ethanolic extracts of the plants on the basis of the doses used by the Phytofla Laboratories.

Administration of the vehicle (0.5% aqueous-ethanol) did not change plasma glucose after three (3) hours. Plasma glucose remained stable. Metformin administered at 500 mg/kg body weight significantly lowered plasma glucose levels from 5.85±0.59 mmol/L to 4.26±0.20 mmol/L (Table 1). Administration of the different aqueous ethanolic extracts (*G. sylvestre*, *S. birrea* or combination) did not significantly change the basal plasma glucose. Extracts compared to the control had no significant effect on basal plasma glucose (Table 1).

Aqueous ethanolic extracts of *G. sylvestre* and *S. birrea* leaves administered to normoglycemic mice reduced plasma glucose by 7.57 and 0.54%, respectively. The combination of the two extracts decreased more to 17.94%, 3 h after administration. Reducing plasma glucose level can account for facilitating the effects of insulin, delaying intestinal absorption of glucose as do metformin, preventing resorption of glucose as alpha glucosidase inhibitors or stimulating release of insulin like secretagogue substances (Gong et al., 2012).

Reducing basal glycaemia by plants extracts is not statistically significant at the tested dose. This suggests weak risk of hypoglycemia with either extract in our conditions of use.

Ojewole[a] (2003b) showed that the aqueous extract of *S. birrea* stem bark used at 800 mg/kg in rats had a hypoglycemic effect on basal plasma glucose after one hour of treatment. The maximum percentage of plasma glucose reduction was 27.98% after 8 h of treatment**.** This difference could be due to the difference in the organ of the plant used, the dose used and the type of extract.

Effect of aqueous ethanolic extracts of *G. sylvestre* leaves on oral glucose tolerance

Oral glucose tolerance test with 20% glucose solution in mice fasted for 14 h resulted in hyperglycemia with a peak of 15.13 ± 1.27 mmol/L 30 min after administration. That peak was significantly prevented by metformin administered 90 min before charge of glucose ($P < 0.001$) (Figure 1). The aqueous ethanolic extract of *G. sylvestre* leaves at 100 mg/kg body weight but not at 12.5 or 25 mg/kg body weight, significantly ($p<0.05$) decreased the peak of hyperglycemia by 21% (Figure 1).

Secondary metabolites in medicinal plant like tannins, flavonoids, alkaloids and saponosides are reported to have an anti-diabetic property (Saneja et al., 2010; Kumari and Jain, 2012; Kebièche et al., 2011). Also secondary metabolites occurring in common consumed (Pascale et al., 2018; Bianco et al., 2018). These compounds were founded in the aqueous ethanolic extract of the leaves of *G. sylvestre*. In previous study,

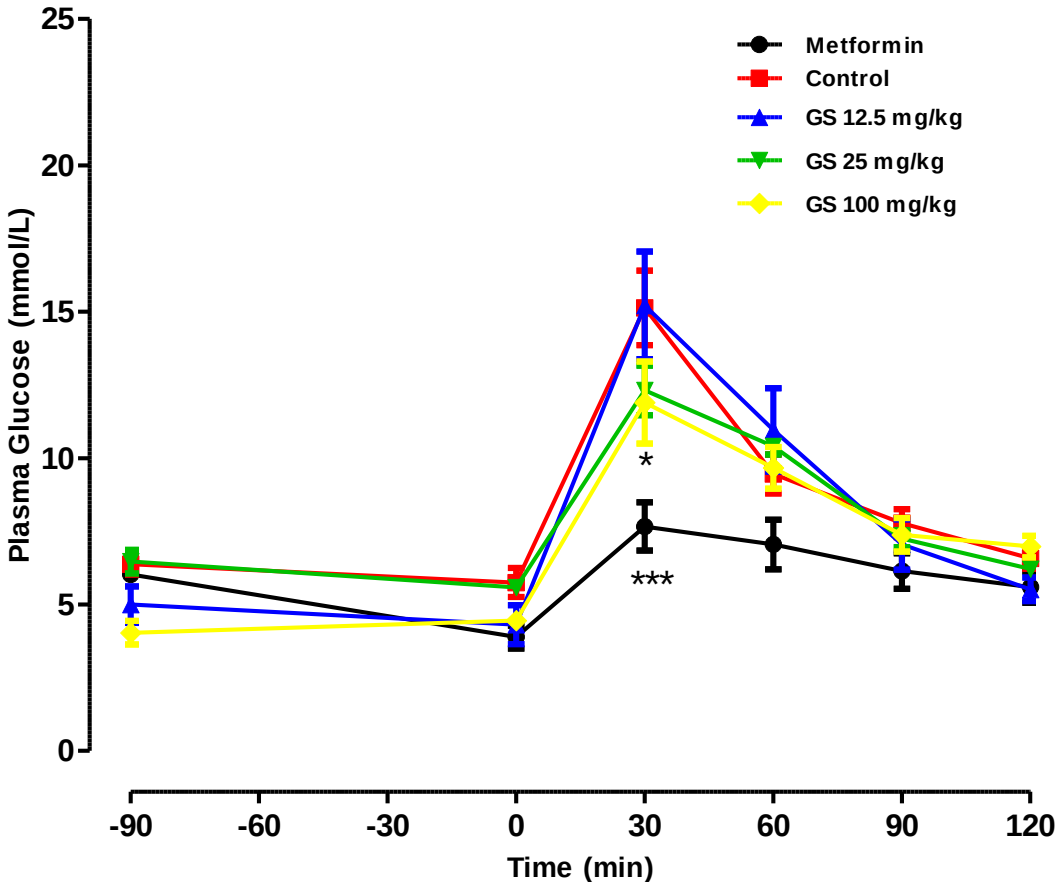

Figure 1. Effect of aqueous ethanolic extract of *Gymnema sylvestre* (GS) leaves on oral glucose tolerance. *p<0.05 and ***p<0.001 significant different from control group.

we elucidated that flavonoids such as quercetin, potentiate insulin secretion and protect INS-1 pancreatic β-cells against oxidative damage via the ERK ½ pathway (Youl et al., 2010). In addition, the insulin-secretory effect of quercetin is mediated by direct activation of L-type calcium channels in pancreatic β-cells (Bardy et al., 2013). Tannins (Pinent et al., 2004), saponosides and alkaloids may also cause the peak of hyperglycemia to drop. Indeed, studies have shown that the main active component of *G. sylvestre* is gymnemic acid, a saponoside of the triterpene group. Gymnemic acid would (1) promote regeneration of islet cells, (2) increase secretion of insulin, (3) cause inhibition of glucose absorption from the intestine, (4) increase utilization of glucose, decrease in gluconeogenic enzymes and sorbitol dehydrogenase (Saneja et al., 2010). Alkaloids would decrease post-prandial plasma glucose (Kebièche et al., 2011). A triterpene glycoside (TG) fraction isolated and purified from ethanolic extract of *G. sylvestre* was also investigated for blood glucose control benefit (Shenoy et al., 2018).

G. sylvestre leaves have been used for millennia in India for its anti-diabetic properties. Leaves extract of the plant has been reported to reduced significantly plasma glucose in animal model of chronic diabetes of Grijesh et al. (2009) and Vijayanand et al. (2012).

Effect of aqueous ethanolic extracts of *S. birrea* (SB) leaves on oral glucose tolerance

The aqueous ethanolic extract of *S. birrea* leaves at the dose of 12.5 and 25 mg/kg body weight, did not significantly reduce the peak of hyperglycemia. However, the dose of 100 mg/kg body weight resulted in a significant inhibition of the peak of hyperglycemia ($p < 0.001$) by 36% (Figure 2).

The effect could be explained by the richness of the extract in tannins, saponosides and flavonoids. Russo in 2018 showed antiradical activity of methanol extract from the leaves of *S. birrea* against the investigated physiological radicals in a dose-dependent manner (Russo et al., 2018).

Kebièche et al., (2011) working on the anti-diabetic activity of *Ranunculus repens L.* proved that flavonoids would act by storing plasma glucose in peripheral tissues

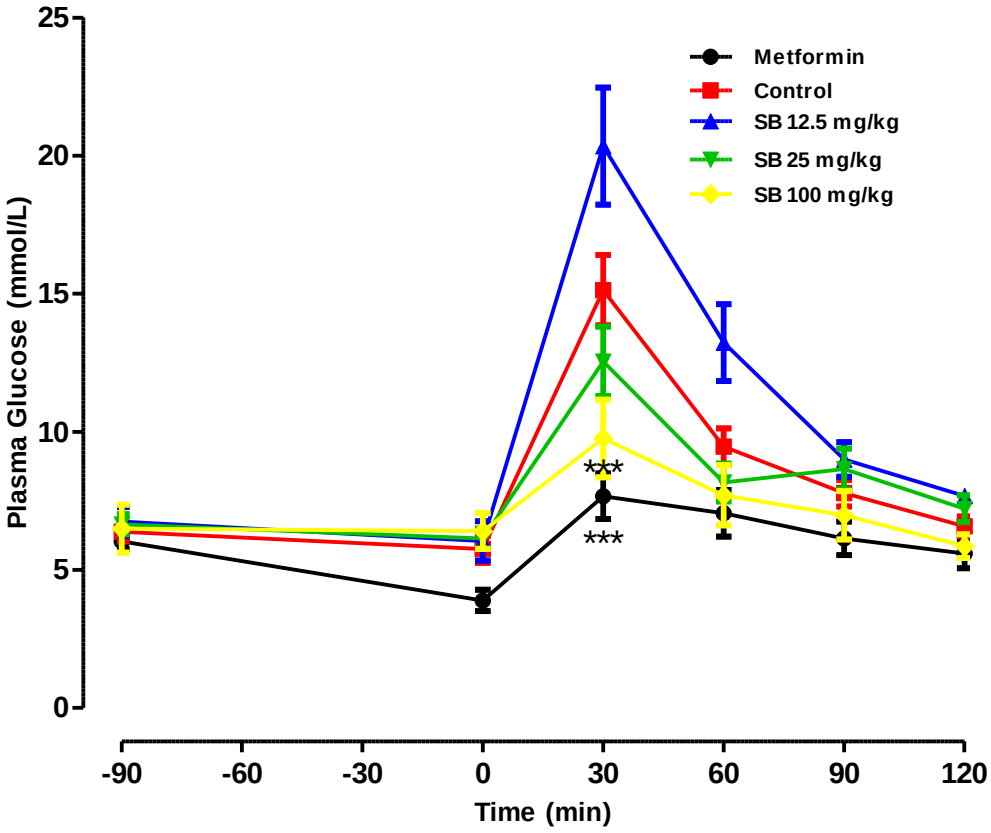

Figure 2. Effect of aqueous ethanolic extract of *Sclerocarya birrea* (SB) leaves on oral glucose tolerance. ***p<0.001 significant different from control group.

such as the liver as hepatic glycogen. They would also act by activating the insulinosecretion (Kebièche et al., 2011). In addition, the active compound of *S. birrea* is quercetin (Ojewole et al., 2010). It would act by inhibiting adipogenesis. It would inhibit NF-κB pathway by PPARγ activation (Liu et al., 2016).

Tannins have enzyme-inhibiting, antioxidant properties. In terms of chemical composition, the aqueous ethanolic extract reduces hyperglycemia and could prevent diabetes complications.

S. birrea is a widely studied plant. Its anti-hyperglycaemic activity has been investigated by several authors. Dimo et al. (2007) showed the antihyperglycemic effect of *Sclerocarya birrea* stem bark on a model of chronic diabetes (streptozotocin) and oral glucose tolerance. It appeared that the extract resulted in a significant reduction in blood sugar and an increase in insulin levels (Dimo et al., 2007).

Mogale et al. (2011) studied the inhibitory effects of methanolic, acetonic and hexanic extracts of stem bark on intestinal α-amylases and α-glucosidases. This study showed that the hexanic extract inhibited intestinal α-glucosidases and could therefore be used, in cases of type 2 diabetes, to lower postprandial hyperglycemia (Mogale et al., 2011).

Effect of association of aqueous ethanolic extracts of *G. sylvestre* and *S. birrea* leaves on oral glucose tolerance

In order to point out any synergistic effect on plasma glucose level, the aqueous ethanolic extracts of both *G. sylvestre* and *S. birrea* at equal amount was associated. The combination of extracts at 12.5 mg/kg body weight and 25 mg/kg body weight had no effect on the oral glucose tolerance. However, at 100 mg/kg body weight, the combination significantly reduced the peak of hyperglycemia ($p< 0.001$) to a reduction percentage of 47% (Figure 3).

The combination of the two extracts at 100 mg/kg delayed the onset of the peak (plasma glucose level is higher at 1 h than 30 min). This delay could be explained by inhibition of intestinal absorption of the glucose which mechanism could coexist with another one.

At the dose of 100 mg/kg body per weight, a 21% decrease in the hyperglycemic peak with the *G. sylvestre* extract was obtained, respectively and 36% with the aqueous ethanolic extract of *S. birrea*. The combination of both extracts of plants reduced hyperglycemia by 47%. The reduction of the hyperglycemic peak was accentuated by the combination. The effect observed

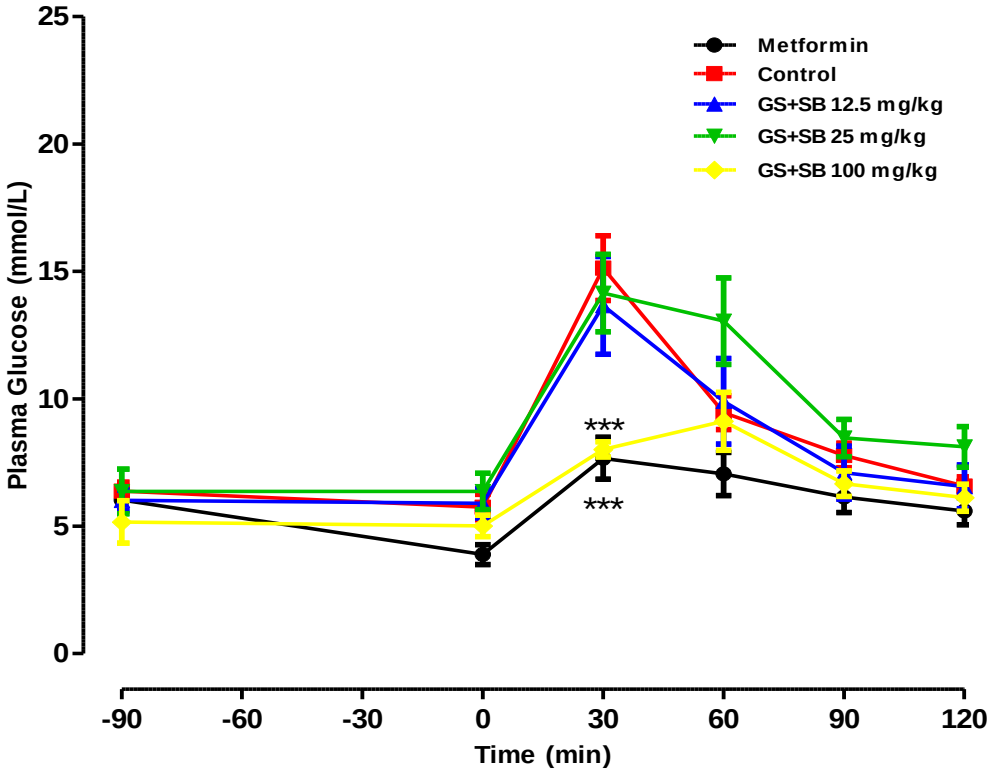

Figure 3. Effect of aqueous ethanolic extracts of *Gymnema sylvestre* (GS) and *Sclerocarya birrea* (SB) leaves on oral glucose tolerance. ***p<0.001 significant different from control group.

with the combination of the two extracts at dose of 100 mg/kg body weight could yield a synergistic effect of hypoglycemic chemical compounds existing in the extracts of leaves of *G. sylvestre* and *S.birrea*. These are flavonoids, saponosides and tannins. In the literature, the researchers did not encounter any work on the antihyperglycemic activity of the aqueous ethanolic extract of *G. sylvestre* associated with *S. birrea*.

Conclusion

The results pointed out an effectiveness of aqueous ethanolic extract of *S. birrea* in preventing peak in glucose overload. That effect was reinforced by co-administration of aqueous ethanolic extract of *G. sylvestre.* Both extracts showed lack of hypoglycemic effect. These effects could support benefit of the phyomedicine, Diabefla and were probably due to chemical compounds in extracts of the plants. Further investigations are necessary to highlight mechanisms and structures of active compounds in both extracts of the plants.

CONFLICT OF INTEREST

The authors have not declared any conflict of interests.

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