

Re-evaluating the efficacy of the aqueous leaf extract of *Bridelia ferrugenia* and its potential combination with metformin in the management of diabetes mellitus

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ABSTRACT

Herbal medicinal products play a significant role in the management of diabetes and other chronic diseases either as a monotherapy or in combination with allopathic treatments. The hypoglycemic activity of a Ghanaian herbal antidiabetic product (Bridelia Tea) prepared from the dried leaves of *Bridelia ferrugenia* [BRD] was re-evaluated in this study with the view of improving, its activity and explore the possible benefit of using the product in combination with metformin (MET). Male and female Sprague-Dawley rats (210-220 g) were rendered hyperglycemic by a single intraperitoneal administration of streptozocin (70 mg/kg) after an overnight fast. The hyperglycemic rats then received one of the following treatments ([BRD 30 mg/kg or 300 mg/kg], [MET 250 mg/kg or 1000 mg/kg], [MET 250 mg/kg and BRD 30 mg/kg], [MET 1000 mg/kg and BRD 300 mg/kg]). The hypoglycemic effect of BRD, MET, and the combination of the two products were not significantly different during an initial 6 h of monitoring ($P > 0.05$). In the long-term study over 28 days, BRD 300 mg/kg had hypoglycemic effects comparable to MET 1000 mg/kg p.o. and better than BDF 30 mg/kg p.o. ($P < 0.05$). However, the combination of the two products BRD and MET at the two doses reduced their therapeutic effect compared to animals receiving either one of the two treatments alone.

KEY WORDS: *Bridelia ferrugenia*, diabetes, herbal medicines, interactive study

INTRODUCTION

Diabetes mellitus, one of the most common endocrine-metabolic disorders has caused significant morbidity and mortality due to micro vascular (retinopathy, neuropathy, and nephropathy) and macro vascular (heart attack, stroke, and peripheral vascular disease) complications (Patel *et al.*, 2011). This potential for multiple end organ damage from diabetes mellitus makes the proper control of blood sugar very critical during the management of diabetics (Blonde 2005). Currently, most individuals with chronic conditions such as diabetes, hypertension, and cancers in the developing countries prefer or rely on some form of traditional therapy. These treatments largely involve the use of herbal medicines alone or in combination with conventional treatments or care. The benefits of such

therapies need to be assessed to ensure treatment goals are attained (Firenzuoli and Gori 2007).

In an earlier clinical study, we reviewed the fasting blood sugar (FBS) of patients treated with an infusion prepared from the coarsely powdered leaves of *Bridelia ferrugenia* [BRD]. It was established from this study that preparation caused a clinically insignificant decline in the FBS of patients using the herbal medicine. The results indicated a decline in FBS of 1.886 (confidence interval: 5.676-1.903) over a treatment period of 1 month (Thomford *et al.*, 2015). Based on that report, a re-assessment of the product was undertaken to review the dosage used toward improving its efficacy and also ascertain the potential benefit of using the product in combination with metformin (MET) for individuals that may opt for such combinations.

METHODS

Plant Materials

The processed and packaged product prepared from the dried coarsely powdered plant material was obtained from the production unit of the Centre for Plant Medicine Research (CPMR).

Extraction

The plant materials were prepared according to the procedure listed out for patients using the product. A hot infusion was made by adding one tablespoon of the powdered leaves of BRD (≈ 6.49 g) in 500 ml of boiling water for 10-15 min and then decanting. The resultant extract had a dry weight of 0.97 g (± 0.20).

Animals Used and Handling

Adult male Sprague-Dawley rats aged between 3 and 4 months and weighing 210-220 g were used for the study. They were housed under standard conditions at ambient temperature and supplied with standard pellets and water *ad libitum* at the animal house of the Department of Pharmacology, CPMR. All rats were handled in accordance with the accepted principles for laboratory animal use and care (EU directive of 1986:86/609/EEC).

Induction of Diabetes in Rats using Streptozotocin (STZ)

The bioassay employed was according to the description of Singh *et al.*, (2001) with some modifications. STZ (0.588 g) was dissolved in freshly prepared 0.1 M citrate buffer solution of pH - 4.5. The blood glucose level of rats before the experiment were taken and found to be in the range of 3.9-4.7 mmol/l. The rats were injected intraperitoneally with a single dose of 70 mg STZ per kg body weight (BW) after an overnight fast. After injection, rats were given free access to food and water. After a rest period of 48 h, hyperglycemia was confirmed by determining the fasting blood glucose levels. The rats with blood glucose levels above 10.0 mmol/l, were selected for the experiment.

Test for Hypoglycemic Activities of BRD

The diabetic rats were randomly divided into six groups of five animals each: Groups A - F. rats in groups A and B were given oral doses of 30 mg/kg and 300 mg/kg BRD p.o., respectively. The 30 mg/kg dose of BRD is equivalent to the current prescribed dose for an adult diabetic patient. The rats in groups C and D received 250 mg/kg and 1000 mg/kg of the standard antidiabetic drug MET.

Group E received the combination of 30 mg/kg BRD and 250 mg/kg of MET. Animals in Groups F were also treated with both 300 mg/kg BRD and 1000 mg/kg MET.

Statistical Analysis

All data provided in this study represent mean \pm standard error mean. The results were analyzed using a one and two-way Analysis of Variance followed by Bonferroni's post-test. Results were considered significant if $P < 0.05$.

RESULTS

The Hypoglycemic Activity of BRD and its Combination with MET

In the 6 hr glucose control monitoring for the various groups, the decline in FBS was not significantly different across the groups (Figure 1). Animals treated with 30 mg/kg BRD recorded a 36.13% (8.02 ± 1.28 mmol/l) decline in their mean FBS over the 6 hr period. The group treated with 300 mg/kg of the BRD also had a 30.32% (6.62 ± 1.38 mmol/l) reduction in mean FBS.

The standard antidiabetic treatment MET resulted in 33.30% (7.36 ± 1.51) and a 47.24% (9.28 ± 3.09 mmol/l) decline in mean FBS for animals treated with 250 mg/kg and 1000 mg/kg, respectively. The combined treatment of MET and BRD also caused a 34.02% (7.26 ± 1.02 mmol/l) decline in mean FBS for animals receiving 30 mg/kg BRD and 250 mg/kg MET. The rats treated with 300 mg/kg BRD and 1000 mg/kg MET had a 26.17% (4.68 ± 1.18 mmol) reduction in their FBS.

The activity observed during the 28-day study indicated that BRD (300 mg/kg p.o.; FBS: 3.65 ± 0.14 mmol/l) had better hypoglycemic effects than BRD (30 mg/kg p.o.; FBS: 5.47 ± 1.21 mmol/l) with $P < 0.05$ and comparable activity to MET (1000 mg/kg p.o.; 2.90 ± 0.06 mmol/l) at the end of the study (Figure 2).

The combination of the two treatments: BRD and MET (30 mg/kg p.o. and 250 mg/kg p.o., respectively) however was lower in therapeutic effect (FBS: 20.0 ± 0.56 mmol/l) when compared to animals receiving only BRD 30 mg/kg p.o. (FBS: 5.47 ± 1.21 mmol/l; $***P < 0.001$) but not significantly different from animals treated with only MET 250 mg/kg p.o. (FBS: 17.15 ± 2.15 mmol/l; $P > 0.05$). Similar effects were recorded for the combination of BRD and MET (300 mg/kg p.o. and 1000 mg/kg p.o., respectively; FBS of 17.88 ± 1.02 mmol/l) compared to rats treated with only BRD

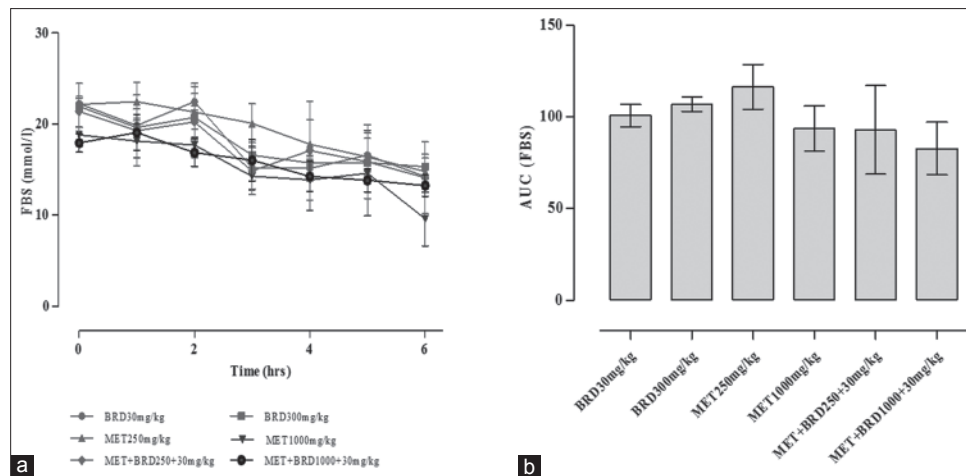


Figure 1: Effect of treatments on the mean fasting blood sugar of rats receiving *Bridelia ferruginea* (BRD) (30 mg/kg p.o.; Group A) BRD (300 mg/kg p.o.; Group B), metformin (MET) (250 mg/kg p.o.; Group C), MET (1000 mg/kg p.o.; Group D), MET + BRD (250 mg/kg and 30 mg/kg p.o.; Group E), and MET + BRD (1000 mg/kg and 30 mg/kg p.o.; Group F) shown on the time course curve (a) and the histogram (b) during the 6 h of glucose monitoring. Data is represented as mean \pm standard error mean, $n = 5$, One and two-way ANOVA compared to BRD (30 mg/kg p.o.) followed by Bonferroni's posttest

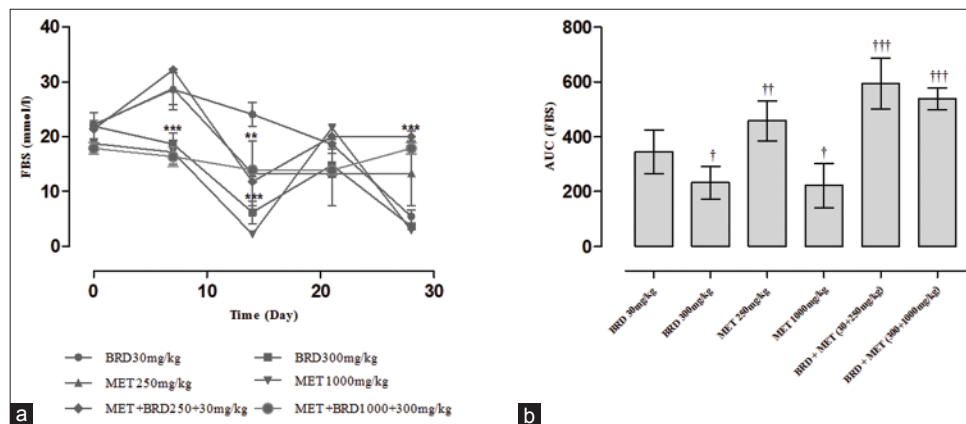


Figure 2: Effect of treatments on the mean fasting blood sugar of rats receiving *Bridelia ferruginea* (BRD) (30 mg/kg p.o.; Group A), BRD (300 mg/kg p.o.; Group B), metformin (MET) (250 mg/kg p.o.; Group C), MET (1000 mg/kg p.o.; Group D), MET + BRD (250 mg/kg and 30 mg/kg p.o.; Group E), and MET + BRD (1000 mg/kg and 30 mg/kg p.o.; Group F) shown on the time course curve (a) and the histogram (b) during the 28 days of follow up. Data is represented as mean \pm standard error mean, $n = 5$, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared to BRD (30 mg/kg p.o.). $\dagger P \leq 0.05$, $\dagger\dagger P \leq 0.01$, $\dagger\dagger\dagger P \leq 0.001$ compared BRD (30 mg/kg) followed by Bonferonni's posttest

300 mg/kg p.o. (FBS: 3.65 ± 0.14 mmol/l; $***P < 0.001$) and those receiving only MET 1000 mg/kg p.o. (2.90 ± 0.06 mmol/l; $***P < 0.001$).

Effect of Treatments on the BW of Diabetic Rat

The BW of animals taken at the baseline (day 0), mid-study (day 14), and the end-of-study (day 28) is reported as Table 1. The normal control recorded a 4.27% increment in their weight. The diabetic controls recorded a 31.64% decline in their BW. Animals receiving BRD 30 mg/kg also had an 11.08% decline with BRD 300 mg/kg having a 9.68% reduction. BW also declined by 10.78% for rats treated with MET 500 mg/kg, 9.54% for MET 1000 mg/kg, 7.44% for MET + BRD (30 + 500 mg/kg), and 9.27% for MET + BRD (300 + 1000 mg/kg).

DISCUSSION

Although BRD had been reported as having antidiabetic properties by some authors (Iwu 1983; Njamen *et al.*, 2012), our previous clinical study indicated otherwise (Thomford *et al.*, 2015). However, the possibility of the dosage, dosage form, and standardization affecting the overall efficacy of the product meant this *in vivo* study had to be undertaken to review the dose of the product; a critical factor affecting the biological effect of botanical treatments (Ahmad *et al.*, 2006).

The current dosage administered to patient visiting the clinic of the CPMR was calculated to be approximately 30 mg/kg representing the minimum dose accessed during

Table 1: Effect of treatments on the body weight of diabetic rat during the study

Treatment group	Day 0	Day 14	Day 28
Normal control	215.49±2.31	227.87±1.51	225.10±3.29
Diabetic control	212.30±1.05	177.19±4.31	145.12±5.37
BRD 30 mg/kg	217.79±0.98	193.66±2.11	183.76±1.98
BRD 300 mg/kg	214.18±1.33	198.32±1.97	193.45±2.37
MET 500 mg/kg	215.31±0.96	197.51±2.07	192.11±3.57
MET 1000 mg/kg	219.74±2.83	199.32±3.11	195.13±4.31
BRD+	214.39±0.64	201.31±0.91	198.45±4.50
MET (30+500) mg/kg			
BRD+	217.59±3.01	203.86±1.91	197.41±1.07
MET (300+1000) mg/kg			

Data is represented as mean±SEM, n=5. Body weights of the diabetic control and the treatment groups with significantly different ($P<0.001$) compared to the normal control on day 14 and 28, SEM: Standard error mean, BRD: *Bridelia ferruginea*, MET: Metformin

this experiment. The hypoglycemic effect of the 2 doses of BRD were significantly different after 28 days (BRD 30 mg/kg p.o. [5.47 ± 1.22 mmol/l] and BRD 300 mg/kg p.o. [3.65 ± 0.14 mmol/l]; $P < 0.05$). The response obtained for the highest dose of BRD was also comparable to animals that received MET only (1000 mg/kg p.o.). These findings indicate that the hypoglycemic effect of the plant may be improved with an increase in the dosage currently administered.

Significantly, the combination of MET and BRD also decreased the therapeutic response obtained during this study implying a possible herb-drug interaction. Some herbal products have been noted to have such interactions with their biological activity noted to affect either the bioavailability, metabolism and/or clearance of allopathic drugs. In some instances, these interactions have been exploited for the benefit of patients as in the case of the administration of Senna and the opioid analgesics during palliative care. Other interactions such as the combined use of St. John's Worts and Warfarin have been reported as potentially dangerous (Agra et al., 1998; McEwen, 2015). Therefore, the negative interaction between BRD and MET, needs to be explored further.

Finally, reformulation of the product from its current dosage form of a powder may have to be considered if the increase in dosage is to be implemented especially to ensure patient compliance.

CONCLUSION

The study has shown that clinical activity of the product may be improved by an increase in the dosage from the current 30 mg/kg to 300 mg/kg. It is also relevant to further study the nature of the herb-drug interaction between BRD and MET.

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