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Effects of flavonoid extract from wonderful Kola (*Buchholzia Coriacea*) seed on antioxidant and liver function biomarkers of fructose fed streptozotocin induced type 2 diabetic albino rats

Amaralam E. C [1,*], Achi N. K [2], Oyedemi S. O [2], Aloh G. S [2] and Ajah O [2]

[1] *Department of Microbiology/Biochemistry, School of Industrial and Applied Sciences, Federal Polytechnic Nekede, Owerri, Imo State, Nigeria.*
[2] *Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike, Abia State. Nigeria.*

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Abstract

Wonderful kola is a wonderful herb with excellent healing powers, the seeds is fast gaining reputation because it appears to be a treatment to nearly all ailments. This study evaluates the potential hepatoprotective and antioxidant effects of oral administration of flavonoid-rich seed extract of Buchholzia coriacea seeds in fructose fed Streptozotocin (STZ)-induced diabetic rats. Twenty-five (25) rats were used for this study. They were divided into five (5) groups of five rats each; normal control, negative control (Streptozotocin (STZ)-induced diabetic), positive control (Glibenclamide), 100mg/kg of body weight seed extract and 500mg/kg of body weight seed extract. The flavonoid seed extract of the plant significantly ($P<0.05$) reduced liver damage caused by STZ, as evidenced by the decreased serum alanine amino transferase and aspartate amino transferase activity, compared to in the group treated with STZ alone. The result of the Superoxide dismutase activity (SOS) shows more antioxidant activity than other antioxidant parameters. However, that of catalase enzyme has the lowest activity as compared to Thiobarbituric acid reactive species (TBARS) and Reduced Glutathione (GSH) activities. All were significantly ($P<0.05$) improved following the treatments of flavonoid extract. In conclusion, the results show that seeds of *Buchholzia coriacea* contain a potent antioxidant and hepatoprotective effects, which can give scientific merit to the traditional use of the extract in the management of diabetes and the improvement of its complications.

Keywords: *Buchholzia coriacea*; Streptozotocin; Flavonoid; antioxidant; Catalase; Superoxide dismutase; Rats

1. Introduction

Type 2 diabetes is a heterogeneous disorder characterized by two interrelated metabolic defects: insulin resistance associated with impaired insulin secretion from pancreatic beta cells (kahn, 2008). Therefore, strategies that target these two mechanisms to improve insulin sensitivity and protect beta cell function have become a priority for prevention efforts. Weight loss and physical activity, as well as certain medications, are thought to improve insulin sensitivity and secretion. Because diabetes is a multifactorial chronic disease, many therapeutic goals and a wide variety of medications can be used in the treatment of diabetes. Currently available diabetes medications, with the exception of developing countries. Therefore, these patients often consult traditional healers who rely heavily on herbal medicines to treat diabetes (ekor, 2014).

People with type 2 diabetes mellitus are more vulnerable to various forms of short-term long-term complications, which often lead to their premature death. This trend of increased morbidity and mortality is observed in patients with type

* Corresponding author: Amaralam EC

2 diabetes mellitus due to the frequency of this type of diabetes, its hidden onset and late recognition, especially in developing countries of resource poor development like Africa (Azevedo, et al., 2008).

Various components of the plant, including *Buchholzia coriacea*, are commonly used as antimicrobial, anthelmintic, antitrypanosomal, hypoglycemic and analgesic agents. A logical next step will be to upgrade the crude product into standardized quality managed drugs for more reliable and safer use. Different parts of the plant are very medicinal. The roots as a stimulant, but are believed to be slightly toxic. Other pats-bark extracts, decoctions of leaves, fruits and flowers – used to treat various diseases. Therefore, his study aims to determine the potential hepatoprotective and antioxidant effects of the flavonoid-rich extract of *Buchholzia coriacea* seeds.

2. Methods

2.1. Plant material

Fresh seeds of *Bucholzia. coriacea* (5 kg) were purchased from at a local market (Relief Market) in Imo State, Nigeria. The seeds were immediately washed to remove soil materials, peeled, pressed and dried in the shade for 1 week on laboratory plates. The dried seeds were ground to powder and weighed.

2.2. Extraction

The ground powdered seeds (800 g) were soaked in 95% methanol for 48 hours with intermittent stirring, and then filtered. Using a rotary evaporator, the filtrate was concentrated by evaporation to dryness under reduced pressure at a temperature of 40 °C. The crude extract of *Bulchhozia coriacea* (BCE), was stored in airtight container in a refrigerator until use.

2.3. extraction of flavonoid (Chu *et al.,* 2002)

Two hundred grams (200 g) were dissolved in 20 ml of 10% H_2SO4 and hydrolyzed by heat in a water bath for 30 min at 100 ^{o}C. The mixture was placed on ice for 15 min for precipitation of the flavonoid aglycones. The flavonoid aglycones were then dissolved in 50 ml of warm 95% ethanol, filtered and concentrated by rotary evaporation at 55^{o} C.

2.4. Experimental animals

The albino rats that was used in the work were purchased from the faculty of veterinary medicine, Michael Okpara University of Agriculture, Nigeria. Animals were housed in animal cages under standard laboratory conditions, allowed free access to standard rat pellets and water. The animals were allowed to acclimatize for 10 days before the start of the experiment.

2.5. Induction of type 2 diabetes

The type 2 diabetes was induced according to the method as described by Rachel and Shahidul (2012).

2.6. Experimental design

Twenty-five albino rats were used for this study and they were randomly assigned groups of five animals each. Group one (1) served as the normal control (only food and water), group two (2) were the diabetic control (STZ plus water and feed only), Group three (3) served as the positive control (glibenclamide plus feed and water only), while groups four (4) and (5), served as a test with the concentrations: 100 mg/kg and 500 mg/kg body weight of the plant extract. All the rats received with the extract for 6 weeks, and were sacrificed 24 hours after the last treatment.

Table 1 Table of Experimental Design

S.N	groups	Number of animals	Treatment (all the administration measurement are in mg/kg body weight)
1.	(Normal control)	5	Receives only pellet and water
2.	(Diabetic control)	5	Streptozotocin 40mg/kg + pellet and water only
3.	(positive drug control)	5	5 mg/kg glibenclamide , pellet and water only
4.	(Test)	5	100 mg/kg of B. coriacea flavonoid extract + pellet
5.	(Test)	5	500 mg/kg of B. coriacea flavonoid extract + pellet

2.7. Biochemical analysis

2.7.1 Antioxidant assays

- Superoxide Dismutase (SOD): The pyrogallol autoxidation method as described by Marklund and Marklund, (1974) was used.
- Catalase activity: The method of Cohen et al., 1970 was adopted
- Reduced Concentration of Glutathione (GSH): Reduced concentration of glutathione was determined by the method described by Ellman (1959).

2.7.2 Liver function assays

Serum Alanine Aminotransaminase (ALT) and Aspartate Aminotransaminase (AST) activity

The method of Reitman and Frankel (1957) was adopted in the determination of ALT and AST activities with commercial Randox kits.

Serum alkaline phosphatase (ALP) activity

Alkaline phosphate in the serum was determined by the method of point-calorimetric Oriakh *et al.,* (2018).

Total serum bilirubin concentration

Total Serum bilirubin was determined by the end point colorimetric method (Jendrassik and Grof, 1938).

Serum Total Protein

The serum total protein was determined by the method of Biuret as described by Flack and Wollen, 1984, using the Randox kit

3. Results

Table 2 Result Showing In-vivo Antioxidant activity of *Bulcholzea coriacea* in Streptozotocin induced type II diabetes in albino rat

GROUPS	SOD(µ/l)	CAT (µ/l)	TBARS (mmol/g)	GSH (µmol/L)
Normal Control	81.83±5.90^{a}	51.64±4.45^{a}	68.96±6.44^{a}	70.03±3.64^{a}
Negative Control	59.76±3.29^{c}	29.93±1.74^{c}	110.46±9.35^{c}	49.93±1.23^{d}
Positive control	70.68±2.17^{b}	41.97±2.06^{b}	85.25±8.99^{b}	65.47±4.45^{ab}
100mg/kg b.w.	61.76±2.02^{c}	29.04±1.90^{c}	103.51±6.20^{c}	53.40±5.03^{cd}
500mg/kg b.w.	70.83±3.42^{b}	33.89±2.89^{c}	91.70±3.89^{b}	59.44±2.75^{bc}

Result Showing In-vivo Antioxidant activity of *Bulcholzea coreasea* in Streptozotocin induced type II diabetes in albino rats. Superoxide dismutase (SOD), Catalase (CAT), Thiobarbituric acid reactive species (TBARS) and Reduced Glutathione (GSH); Treatments with superscripts a,b,c,d showed significant difference ($p < 0.05$) compared with the diabetic control rat group. While the superscripts shows that they are not significantly different.; ($p > 0.05$). Values are expressed as mean ± standard deviation (n=4).

From the table, the result of the superoxide dismutase activity (SOS) shows a higher antioxidant activity than the other antioxidant parameters in the table. However, the result of the enzyme catalase shows the lowest activity as compared to the activity of Thiobarbituric acid reactive species (TBARS) and Reduced Glutathione (GSH). T he result from the seed extract groups 100 and 500 mg/kg body weight in all the antioxidant parameters in the table records an increase which is significantly different ($P < 0.05$) when compared to the positive control group.

Table 3 The result showing the effect of *Buchholzia coriacea* flavonoid extract on the liver function parameters of fructose-streptozotocin induced type II diabetes in albino rat.

GROUPS	ALT(U/L)	ALP(U/L)	AST(U/L)	TB (µmol/L)	TP (g/L)
Normal Control	67.00±21.62^{a}	85.50±6.25^{a}	108.00±12.96^{a}	2.51±0.31^{a}	6.90±0.31^{a}
Negative Control	91.33±12.22^{b}	116.33±8.02^{c}	176.00±24.76^{c}	4.93±0.23^{d}	3.25±0.31^{c}
Positive control	75.00±6.00^{ab}	96.33±9.45^{ab}	137.00±5.57^{b}	2.94±0.08^{b}	4.91±0.48^{b}
100mg/kg	91.00±2.16^{b}	108.50±13.53^{bc}	142.50±11.03^{b}	3.64±026^{c}	3.34±0.29^{c}
500mg/kg	77.25±7.89^{ab}	102.60±9.75^{bc}	131.50±2.89^{b}	2.84±0.14^{ab}	4.66±0.31^{b}

Result showing the liver function parameters of fructose-streptozotocin induced type II diabetes in albino rat. Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), Aspartase Transferase (AST), Total Protein (TP) and Total Bilirubin (TB); Treatments with superscripts a,b,c,d showed significant difference ($p < 0.05$) compared with the diabetic control rat group. While the superscripts shows that they are not significantly different; ($p > 0.05$). Values are expressed as mean ± standard deviation (n=4).

From the table, the negative control (Diabetic) group recorded increase in all the analyzed parameters. Indicating liver disorders caused by the prevalence of the type 2 diabetes induced by streptozotocin. In addition, it seems that an increase in enzyme activity observed in the test group of 100mg/kg b.w. is significantly different ($p<0.05$) compared to the normal control group; between the three liver enzymes: ALT, ALP and AST. The test group of 500mg/kg b.w. shows the smallest effects in enzyme activity and other liver function parameters; Total Bilirubin and Total Protein in the table which are not significantly different ($p > 0.05$) compared to the (glibenclamide) group.

4. Discussion

Numerous studies have shown that oxidative stress contributes to the progression of diabetes, worsening its symptoms, especially by impairing the action of insulin, thus increasing the severity of its complications. Oxidative stress caused by reactive oxygen species is considered as a common pathophysiology of diabetic complications (panigrahy *et al.,* 2017). Oxidative stress in cells becomes excessive when there is a loss of balance between oxidants and antioxidant defenses (Ahmed, *et al*., 2018). Superoxide dismutase, Catalase and GPx are antioxidant enzymes that deactivate/hydrolyze peroxides and play an important role in strengthening the body's antioxidant defenses. SOD reduces superoxide to H_2O_2 which can be easily reduced to water mainly by CAT and GPx (Robertson, *et al.,* 2003) that the function of all three enzymes are interdependent is shown by the decrease in their activity and the subsequent accumulation of lipid peroxides and a concomitant increase in oxidative stress in diabetic rats (Chaudhry, et al., 2007). This present study on the in vivo antioxidant activity of the flavonoid-rich extract of *Bucholzia. Coriacea* in diabetic rats showed that superoxide dismutase (SOD) exerts more effective antioxidant activity than other enzymatic and non-enzymatic antioxidants parameters. The activity and levels of all antioxidant parameters studied as shown by the results in table 2, which suggest that the plant extract was able to reduce oxidative stress caused by free radical that causes the breakdown of essential cellular molecules. This is consistent with the result reported by Wenbin, *et al*., (2019), who stated that the levels of malondialdyhide MDA and Nitric oxide NO were significantly decreased with the improvement of the activity of the antioxidant enzymes SOD, CAT and GPx in the kidneys, liver and pancrease of diabetic rats treated with Annona reticulate, (L.), ROS can negatively regulate it insulin signaling, which causes the development of insulin resistance in diabetics, which is a risk factors for type 2 diabetes (Erejuwa, 2012). The results correspond to those of *Bucholzia. Coriacea* (EEBC) and the ethanolic faction of *Bucholzia. Coriacea* (BFBC) significantly reduced the levels of serum creatinine, urea, total cholesterol, triacylglycerols and thiobarbituric acid reactive species. The product in diabetic rats, serum superoxide dismutase activity was significantly ($P <0.05$) improved by EEBC, BFBC and glibenclamide treatments.

The results in Table 3, shows that there is a slight increase in the parameters studied in the test groups compared to the normal control. Liver cell damage may have caused cytosolic enzymes (ALT, AST and ALP) leaks into the sinusoids and eventually into the blood. The present study revealed a significant increase in the levels of AST, ALT ALP and TB in the diabetic control rats (without treatment) compared to the normal control. This is the same with Ohaeri (2001), induction of diabetes with STZ resulted in hepatic necrosis in rats. Therefore, the observed increase in AST and ALT activity must be due to the leakage of these aminotransferase enzymes from the hepatic cytosol into the blood (Navarro *et al.,* 1993), which indicates the hepatotoxic influence of STZ. The decrease in liver function parameters is an indication that the plant extract has the ability to reduce the progression of type 2 diabetes mellitus, because it reduces the risk of developing non-alcoholic fatty liver disease. Condition in which fat accumulates in the liver even if you drink little or no alcohol. However, this supports the claim of Du-Bois Asante et al., (2016) that ethanol extracts of young and old leaves

Vernonia amygdalina significantly ($p < 0.05$) reduced serum ALT, AST and ALP levels compared to diabetic control rats. The results from this study showed that the administration of flavonoid from seed extract of *Buchholzia coriacea* to streptozotocine-induced diabetic rats at the experimental doses and the duration of administration revealed that the extract had antioxidant effect, which can scavenge the action of free radicals and hepatoprotective effects.

5. Conclusion

The results from this study indicated that administration of flavonoid from seed extract of *Buchholzia coriacea* to streptozotocine-induced diabetic rats at the experimental doses and the duration of administrations showed that the extract decreases the liver function parameters and it is an indication that the plant extract has the ability to reduce the progression of type 2 diabetes, as it reduces the risk of developing non-alcoholic fatty liver disease. The elevation in the antioxidant (enzymatic and non-enzymatic) made it a strong agent in the inhibition of reactive oxygen species that caused oxidative stress.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All experiments on animals were in accordance with the guidelines of both the University's ethical committee (Michael Okpara University of Agriculture, Umudike, Abia State) and the International Guidelines for Handling of Laboratory Animals

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