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In vitro screening for protein tyrosine phosphatase 1B and dipeptidyl peptidase IV inhibitors from selected Nigerian medicinal plants

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ABSTRACT

Background/Aim: Protein tyrosine phosphatase 1B (PTP 1B) and dipeptidyl peptidase IV (DPP IV) have been identified as one of the drug targets for the treatment of Type-2 diabetes. This study was designed to screen for PTP 1B and DPP-IV inhibitors from some Nigerian medicinal plants. **Materials and Methods:** PTP 1B and DPP-IV drug discovery kits from Enzo Life Sciences were used to investigate *in vitro* inhibitory effect of crude methanolic extract of 10 plants; *Mangifera indica, Moringa oleifera, Acacia nilotica, Arachis hypogaea, Senna nigricans*, *Azadirachta indica, Calotropis procera, Leptadenia hastata, Ziziphus mauritiana,* and *Solanum incanum.* **Results:** The results indicated PTP IB inhibition by *S. nigricans* (68.2 ± 2.29%), *A. indica* (67.4 ± 2.80%), *A. hypogaea* (57.2 ± 2.50%), *A. nilotica* (55.1 ± 2.19%), and *M. oleifera* (41.2 ± 1.87%) were significantly ($P < 0.05$) higher as compared with standard inhibitor, sumarin while that of *L. hastata* (18.1 ± 2.00%) was significantly lower as compared with sumarin. The PTB 1B inhibition by *M. indica* (31.5 ± 1.90%) was not significantly ($P > 0.05$) different from that of sumarin. The DPP-IV inhibition by *S. incanum* (68.1 ± 2.71%) was significantly higher as compared with a known inhibitor, P32/98. *S. nigrican* (57.0±1.91%), *Z. mauritiana* (56.6±2.01%), *A. hypogaea* (51.0±1.30%), *M. indica* (44.6 ± 2.40%), *C. procera* (36.2 ± 2.00%), *A. nilotica* (35.4 ± 2.10%), and *A. indica* (33.6 ± 1.50%) show significantly ($P < 0.05$) lower inhibitions toward DPP-IV. **Conclusion:** The work demonstrated that these plant materials could serve as sources of lead compounds in the development of anti-diabetic agent(s) targeting PTP 1B and/or DPP-IV.

KEY WORDS: Dipeptidyl peptidase IV, inhibition, medicinal plants, protein tyrosine phosphatase IB, Type-2 diabetes mellitus

INTRODUCTION

Herbal medicines have gained popularity worldwide due to their natural sources, low-cost, and less toxicity. There are several plant species that have been reported to have antidiabetic effect in diabetic animal models [1-5] and humans [6]. In Nigeria, *Mangifera indica, Moringa oleifera, Acacia nilotica, Arachis hypogaea, Senna nigricans*, *Azadirachta indica, Calotropis procera, Leptadenia hastata, Ziziphus mauritiana,* and *Solanum incanum* are being used traditionally for the treatment of diabetes mellitus, but very little is known about the mechanism of actions of antidiabetic activity of these medicinal plants. However, reports show that a number of bioactive ingredients such as flavonoids [7], alkaloids [8], and saponin [9] have been reported to exert antidiabetic activity. Ojiako *et al.* [10] stated that interplay of these bioactive constituents in medicinal plants could be responsible for the hypoglycemic effect. Extracts of *M. indica* [11], *A. hypogaea* [12,13], *A. nilotica* [14], *A. indica* [15], *L. hastata* [16], *Z. mauritiana* [17], *C. procera* [18], and *M. oleifera* [19] have been reported to possess antidiabetic effects. Recently, efforts are being made toward elucidating the mechanism of actions of some of these medicinal plants and their active constituents.

Diabetes mellitus and its associated complications are the major cause of morbidity and mortality worldwide [20]. In particular, Type-2 diabetes mellitus is the most prevalent form of diabetes accounting for more than 80-90% of the total cases of diabetes [21,22]. Type-2 diabetes mellitus is associated with both macrovascular and microvascular complications that may result in tissue or organ damage. It is estimated that about 415 million people have diabetes in the world and more than 14 million cases in sub-Saharan African [23]. It is expected that this figure would be double in 2040. In Nigeria, there were more than 1.56 million cases of diabetes in 2015 and number of deaths related to adult diabetes (20-79 years) were estimated to be 40,815 [23].

Protein tyrosine phosphatases (PTB) are large family of surface proteins that are central modulators of tyrosine phosphorylation-dependent cellular activities [24,25]. Dipeptidyl peptidase IV (DPP IV) is a proteolytic enzyme that specifically deactivates glucagon-like peptide -1 (GLP-1), an incretin hormone which plays a significant role in the regulation of blood glucose level by stimulating the secretion of insulin, increasing β-cell mass and inhibit the secretion of glucagon [26]. PTP 1B and DPP-IV have been recognized as the best drug target for treatment of Type-2 diabetes mellitus [27,28]. Inhibition of PTP 1B increased the rate of phosphorylation of the insulin receptor and its substrate thereby promoting glucose transporters for the uptake of glucose by insulin sensitive cells while DPP-IV inhibitors maintain the level of active GLP-1 [26,28]. Therefore, medicinal products which contain essentially vast bioactive diversity may serve as potential sources of novel inhibitor(s) of PTP 1B and DPP-IV for the treatment of Type-2 diabetes mellitus. The study was designed to screen medicinal plants with PTP IB and DPP-IV inhibitory activities.

MATERIALS AND METHODS

Chemicals and Reagents

PTP IB and DPP-IV drug discovery assay kits used were products of Enzo® Life Sciences and other chemicals and reagent used were of analytical grade.

Plant Materials

A total of 10 plant materials were screened. These included plant extracts studied in our laboratory with *in vivo* hypoglycemic activities and other plant materials that are used by traditional medical practitioners in Northwest Nigeria for the management of diabetes mellitus. Information about antidiabetic plants was sourced by oral interview of traditional medical practitioners, diabetic patients using some of these plants and the general public. In this respect, the following plants were used (Table 1).

The plant materials were collected from farms around Sokoto, Katsina and Kwara States of Nigeria. The plant materials were identified and authenticated by a Taxonomist, Dr. Umar Abdullahi, from Botany Unit, Department of Biological Sciences, Usmanu Danfodiyo University, Sokoto Nigeria. Voucher specimens were deposited at the herbarium of the same institution.

Sample Preparation

The samples were shade dried and ground to powder using laboratory pestle and mortar, except groundnut seeds. The dried, ground powdered materials were stored in paper bags in desiccators until required. Ten g of the powdered samples were extracted in 100 mL of methanol for 72 h at room temperature, in brown cleaned reagent bottles, with intermittent mixing. At the end of the 72 h, the extracts were filtered using Whatman No. 1 filter paper. The filtrates were concentrated using rotary evaporator, and the concentrated filtrates were left to dryness in a drying cabinet and the materials obtained were stored in air tight labeled container at 4°C for further analysis. The groundnut seeds were soaked in distilled water for about 3 h and the extract filtered and the dissolved solutes (% w/v) determined. The extracted materials were reconstituted in DMSO at 10 mg/ml and used for the preliminary screening for PTP 1B and DPP-IV inhibitory activities.

PTP 1B Inhibition Assay

The kit components were thawed on an ice bath with the exception of BIOMOL RED™ that was stored at room temperature. The substrate ('IR5' Insulin receptor β, residues 1142-1153, Py1146) was reconstituted to a concentration of 1.5 mM by assay buffer and distilled H_2O. The assay buffer, 100 mM MES, pH 6.0 containing 300 mM NaCl, 2mM EDTA, 2 mM DTT and 0.1% NP-40 was diluted with equal volume of distilled H_2O and maintained on ice. The PTP 1B (human recombinant) was prepared in ×1 cold assay buffer. Stock of 10 mM of suramin (a known inhibitor) was prepared in assay buffer. The assay mixture was prepared in 96 well plate which contains 10 μg per 100 μL assay mixture of the sample. The plate reader was read at 620 nm, and all the assay protocol was done in accordance with manufacturer's instructions.

DPP IV Inhibition Assay

The crude extracts were screened for DPP-IV inhibition at 100 μg/mL in a total volume of 100 μL using DPP-IV drug discovery assay kits. The inhibitor (P32/98) was diluted in the assay 1 in 10 buffer (50 mM Tris, pH 7.5). The substrate (H-Gly-Pro-pNA) and DPP IV (BML-SE434-9090) were diluted in 1 in 50 μL of the assay buffer. The plant samples were reconstituted in 50 mM Tris buffer, pH 7.5, to give 1 μg/μL. The assay mixture was prepared in 96 well plates which contains 10 μg per 100 μL assay mixture of the sample. The assay mixture consists of 15 μL of DPP IV (17.3 μU/μl) and 50 μL of the substrate and was made up to 100 μL with the assay buffer while P32/98 was used in the place of extracts as a control. The blank was prepared using the substrate and the buffer only. The plate was read continuously at 405 nm, in a microplate reader at 1 min interval for 10 min. The percentage inhibition of the two enzymes by test extracts was calculated based on the activity in control well as 100% from three independent replicates.

Table 1: Medicinal plants screened

Botanical Name	Part used	Voucher number
Mangifera indica	Leaf	UDUS/VS/2011/30
Azadirachta indica	Leaf	UDUS/VS/2011/34
Moringa oleifera	Leaf	UDUS/VS/2011/31
Acacia nilotica	Seed	UDUS/VS/2011/32
Calotropis procera	Leaf	UDUS/VS/2011/28
Leptadenia hastata	Leaf	UDUS/VS/2011/35
Ziziphus mauritiana	Leaf	UDUS/VS/2011/36
Solanum incanum	Fruit	UDUS/VS/2011/22
Senna nigricans	Leaf	UDUS/VS/2011/33
Arachis hypogaea	Whole seed	UDUS/VS/2011/24

Data Analysis

The values are expressed as mean percentage inhibition ± standard deviation. The mean percentage inhibition was analyzed using one-way ANOVA with SPSS (Version 17.0), and $P < 0.05$ was considered statistically significant.

RESULTS

The results of the percentage inhibition of PTP 1B and DPP-IV of the crude methanol extract of medicinal plants used in the Northwest Nigeria are presented in Tables 2 and 3, respectively. The result shows that *S. nigricans* and *A. indica* show the highest PTP 1B inhibition of 68.2 ± 2.29% and 67.4 ± 2.80%, respectively, followed by *A. hypogaea* (57.2 ± 2.58%), *A. nilotica* (55.1 ± 2.19%), *M. oleifera* (41.2 ± 1.87%) which were significantly ($P < 0.05$) higher as compared with sumarin (30.1 2.00%). The PTP IB inhibition by *M. indica* (31.5 ± 1.90%) was not significantly ($P > 0.05$) different as compared with the standard inhibitor, sumarin while *L. hastata* with the least inhibition of 18.1 ± 2.00%. *C. procera, S. incanum,* and *Z. mauritiana* show no inhibition against PTP 1B activity which could serve as activators.

The results for DPP-IV inhibition indicated that *S. incanum* (68.1 ± 2.71%) was significantly ($P < 0.05$) higher as compared with a known inhibitor, P32/98 (63.1 ± 2.70%) while inhibition activity by *S. nigricans* (57.0 ± 1.91 %), *Z. mauritiana* (56.6 ± 2.01%) *Arachis hypogaea* (51.0 ± 1.30), *M. indica* (44.6 ± 2.40), *C. procera* (36.2 ± 2.00), *A. nilotica* (35.4 ± 2.10), and *A. indica* (33.6 ± 1.50%) were significantly ($P < 0.05$) lower as compared with P32/98. There was no inhibition of DPP-IV activity by *L. hastata* and *M. oleifera* which suggest the plants could act as activators of the enzyme.

Table 2: Percentage inhibition of crude methanol extract of different medicinal plants against PTP 1B

Plant materials	% inhibition
Mangifera indica	31.5±1.90
Azadirachta indica	67.4±2.80*
Calotropis procera	NI
Acacia nilotica	55.1±2.19*
Leptadenia hastate	18.1±2.00*
Solanum incanum	NI
Ziziphus mauritiana	NI
Senna nigricans	68.2±2.29*
Moringa oleifera	41.2±1.87*
Arachis hypogaea	57.2±2.58*
Sumarin	30.12±2.00

Data are expressed as Mean±SD, n=3 replicate, NI- no inhibition,*$p<0.05$ when compared with sumarin, standard inhibitor PTP 1B: Protein tyrosine phosphatase 1B

Table 3: Percentage inhibition of crude methanol extract of different medicinal plants against DPP IV

Plant materials	% inhibition
Mangifera indica	44.6±2.40*
Azadirachta indica	33.6±1.50*
Calotropis procera	36.2±2.00*
Acacia nilotica	35.4±2.10*
Leptadenia hastate	NI
Solanum incanum	68.1±2.71*
Ziziphus mauritiana	56.6±2.01*
Senna nigricans	57.0±1.91*
Moringa oleifera	NI
Arachis hypogaea	51.0±1.30*
P32/98	63.1±2.70

Data are expressed as Mean±SD, n=3 replicate, NI- no inhibition, *$p<0.05$ when compared with P32/98, standard inhibitor DPP IV: Dipeptidyl peptidase IV

DISCUSSION

The treatment of diabetes mellitus is considered a global challenge and evaluation of plant products with the aim of isolating antidiabetic agents is gaining popularity worldwide due to the presence of several bioactive constituents with minimal side effect. Selective inhibition of PTB 1B and DPP-IV has been suggested as novel therapeutic target for the treatment of Type-2 diabetes mellitus. In this study, inhibitory activities of ten medicinal plants on PTP 1B and DPP-IV were investigated. The result indicated that *S. nigricans*, *A. indica, A. hypogaea*, *A. nilotica*, *M. oleifera, M. indica,* and *L. hastata* possess significant potentials as sources of lead compounds for the development of PTP 1B inhibitors for the management of Type-2 diabetes mellitus. Similarly, *S. incanum, S. nigricans, Z. mauritiana, A. hypogaea, M. indica*, *C. procera, A. nilotica* and *A. indica* were active against DPP IV, which may serve as sources of inhibitors of the enzyme in the treatment of Type-2 diabetes mellitus. Natural inhibitors like berberine, an isoquinoline alkaloid has been reported to possess potent antidiabetic properties via inhibition of PTP 1B [29-31] and DPP-IV [32]. Papaverine, a structural analog of berberine which belongs to member of isoquinoline alkaloids have also been reported to exhibit potent PTP 1B inhibitory activity thereby lowering fasting blood glucose level *in vivo* [33]. Hydroalcoholic extracts of *Terminalia arjuna* and *Commiphora mukul* have been shown to possess significant DPP-IV inhibitory activity [34]. Although hypoglycemic effects of some of these plants screened have been reported, the mechanism of action has not been fully elucidated. It may be interesting to study whether the antidiabetic effect of these plants extracts acts via inhibition of PTP IB and/or DPP IV activities. Therefore, PTP 1B and DPP-IV inhibitory activities of some of these plants observed in this study indicate that they may serve as potent sources of hypoglycemic agent(s) for the treatment of Type-2 diabetes mellitus. Overexpression of PTP 1B is associated with the development of insulin resistance which could lead to Type-2 diabetes mellitus and obesity [35]. Of all the plants studied, *S. nigricans* had shown to be a better inhibitor of PTP 1B while *S. incanum* had a better effect against DPP-IV. The data reported in this study have shown that *S. nigricans, A. nilotica, A. hypogaea, A indica,* and *M. oleifera* are better inhibitors of PTB 1B than a known inhibitor, sumarin.

Furthermore, going by the result obtained it may be interesting to further exploit these natural products to investigate *in vivo* hypoglycemic effect, study the kinetics of the two enzymes and possibly isolate and characterize the bioactive component(s)

responsible for the inhibition. *S. nigricans* which have shown to be a better source of inhibitor of PTP 1B and to some extent DPP-IV inhibitors could be very promising sources of lead compound(s) for the treatment of Type-2 diabetes mellitus.

CONCLUSION

The results of this work indicated that these plants possess either inhibitory activity against PTP 1B and/or DPP-IV. *S. nigricans* possess significant potentials as sources of lead compound(s) in the development of inhibitors for PTP 1B and to some extent DPP-IV than others. It can then be concluded that these plant materials could serve as sources of lead compounds in the development of antidiabetic agent(s) targeting PTP 1B and/or DPP-IV.

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