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Original Research Article

Effects of Selected *Terminalia* and *Ficus* Species in the Inhibition of *α*-Amylase and *α*-Glucosidase Enzymes

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ABSTRACT

Some *Ficus* and *Terminalia* species are relevant in the management of diabetes mellitus but their antidiabetic principles and mechanism of action are yet to be investigated. This study was aimed at investigating the inhibitory potential of ten ethnobotanically selected *Ficus* and *Terminalia* species against α-amylase and α-glucosidase enzymes. The methanol extracts of ten selected plants from *Ficus* and *Terminalia* genera were tested for their inhibitory activity against porcine pancreatic α-amylase and α-glucosidase from *Saccharomyces cerevisiae* using colorimetric assay. Acarbose was used as the standard. Percentage inhibition was determined and IC_{50} value was calculated by analyzing dose-response data using non-linear regression with the aid of GraphPad prism® (7). The result showed that six plant extracts inhibited α-amylase enzyme while all the ten extracts displayed inhibition against glucosidase enzyme in a concentration-dependent manner. *Terminalia mollis*, *F. capensis*, and *F. vogelli* leaf extracts showed significant ($p<0.05$) inhibitory activity on α-amylase enzyme with IC_{50} of 344.47±4.66, 343.73±6.13; and 1630.67±2.85 µg/mL, respectively, compared to other extracts. A significant inhibitory activity of these extracts was also observed against α-glucosidase enzyme with IC_{50} of 6.482±0.61, 11.36±1.01, and 78.47±1.94 µg/mL, respectively, compared to acarbose IC_{50} 2584±9.61 µg/mL. The results from this investigation justify the folkloric usage of these plants for the management of diabetes mellitus. Hence, further investigation is ongoing to isolate and characterize the antidiabetic principles from *T. mollis, and F. capensis* methanolic leaf extracts.

Keywords: *Terminalia, Ficus*, alpha-amylase, alpha-glucosidase, diabetes mellitus

Introduction

Diabetes mellitus is one of the public health issues of the 21st century, affecting both global health and socio-economic development [1]. It is a chronic metabolic disorder characterized by high plasma glucose levels as a result of deficiency in the release of insulin, insulin action or both. [2] Currently, 537 million people worldwide are affected by diabetes, and this figure is expected to elevate to 643 million by 2030, then by 2045 would have increased to 783 million. [3] The classification of diabetes can be in three types depending on the way it develops: type 1 diabetes (T1D), type 2 diabetes (T2DM) and gestational diabetes. [4] Globally, there is an increasing prevalence of T2DM, it accounts for more than 90 percent of all cases of diabetes worldwide.[5,6] It is characterized by resistance to insulin production and increasing decline of pancreatic β-cell function associated with increasing hyperglycaemia. [7]

Postprandial hyperglycaemia is among the first signs of abnormal glucose homeostasis associated with type 2 diabetes and is evidently overestimated in diabetic patients with fasting high glucose level. [8] Macrovascular and microvascular diabetic complications such as, neuropathy, retinopathy, and nephropathy have been linked to postprandial hyperglycaemia.[9]

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Recently, there has been increasing evidences that postprandial hyperglycaemia contributes majorly to overall control of glucose, depicting a primary target to improve glycated haemoglobin (HbA1c) levels. [10,11] Thus, a reduction in postprandial glycemic excursions contributes to both the maintenance of glucose homeostasis and the longer-term development and progression of the complications of diabetes.[12]

The uptake of dietary carbohydrate has been reported to lead to increased postprandial blood glucose.[13] Involved in the breakdown of carbohydrates are two major enzymes, namely α-amylase and α-Glucosidase.[14] Complex dietary carbohydrates are hydrolysed by alpha-amylase to disaccharides and oligosaccharides with further conversion into monosaccharides by α-glucosidase. Glucose released is then absorbed by the gut leading to postprandial glycemic increase. [15,16] One of the therapeutic strategies in controlling postprandial hyperglycemia is to inhibit enzymes responsible for the hydrolysis of carbohydrate. [16] There is delay in the carbohydrate digestion time by the inhibitors of these enzymes, thereby reducing the glucose absorption rate and as a result bringing down the rise in postprandial plasma glucose.[z4] Examples of drugs currently in use clinically include voglibose, miglitol, acarbose, nojirimycin and 1-deoxynojirimycin.[17] However, some side effects including meteorism, bloating, diarrhea, flatulence, and abdominal distention. [18] Therefore, there is a need for continuous search for drugs from plant source with little or no side effect.

Several species of medicinal plants have been used in the traditional herbal medicines of many cultures throughout the world to treat diabetes. Several studies have revealed that a number of them possess antihyperglycemic properties by inhibiting carbohydrate hydrolyzing enzymes. Therefore, plant-derived natural inhibitors can provide effective treatment for postprandial hyperglycemia without or with minimal unwanted side effects. [19]

This study was aimed at investigating the inhibitory potential of some ethnobotanically selected *Terminalia* and *Ficus* species on carbohydrate hydrolyzing enzymes for their antidiabetic properties.

Materials and Method

Chemicals and reagents

Porcine pancreatic *α*-amylase enzyme, dinitrosalicylic acid, *α*-Glucosidase (*Saccharomyces cerevisiae*) and P-nitro phenyl *α*-D-glucopyranoside (purchased from Sigma-Aldrich), sodium potassium tartrate tetrahydrate, sodium hydroxide, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dodecahdrate, potato starch, acarbose (Glucobay 50 mg tablet), plant extracts (10), distilled water, P_H meter, eppendorf tubes, micropipette (20- 200 µl), 96 well microplate, incubator and ELISA microplate reader.

Plant materials

Nine (9) Plant materials were collected from university of Ibadan botanical garden located at 7˚26' North and 3˚54' East and one (1) was collected from Lokoja, Kogi State June 2, 2021. Six species of the collected plants belong to the genus *Ficus* (Moraceae) while the remaining 4 species belong to the genus *Terminalia* (combretaceae). Voucher specimen of these plants were deposited at the University of Ibadan Herbarium (UIH), Department of Botany, University of Ibadan, Ibadan where they were identified and authenticated. The different parts of plant used for the study and the voucher number allocated to each of deposited specimen is represented in Table 1. Plant materials were subjected to air drying and dried plant materials were pulverized into fine powder using electric milling machine.

Extraction of plant materials

Extraction of pulverized plant materials was carried out using the cold maceration method and methanol was used as extracting solvent. A quantity of 50 g of powdered *T. mantaly, T. ivorensis, F. exasperata, F. vogelii, F. asperifolia, T. catappa* and *T. mollis* were macerated in 500 mL of methanol while 25.2 g of powdered *F. mucuso*, 31 g of *F. pumila* and 28.3 g of *F. capensis* were macerated in 252 mL, 310 mL and 283 mL of methanol, respectively. These were frequently agitated for 72 hours and then filtered. The extracts obtained were concentrated with the aid of a rotary evaporator under reduced pressure at 40 °C and were further evaporated to dryness to obtain a solid mass extract.

Alpha Amylase Inhibition assay

The crude extracts and standard drug solutions were prepared in DMSO. A stock solution of 1000 µg/mL was prepared and serial dilutions were made for the following concentrations 500, 250, 125, 62.5, 30.25 and 15.625 µg/mL and 250, 125, 62.5, 30.25 and 15.625 µg/mL for samples and standard drug, respectively. Acarbose was used as the positive control while the negative control was represented as 100% enzyme activity without the test samples. Blank samples were replaced with buffer solution. Alpha amylase inhibitory activity of the extracts were established in accordance to a reported method by *Karakaya et al*. [20]. Assay was carried out in triplicate and percentage inhibition was calculated as follows:

$$\%\ inhibition = \left(1 - \frac{\Delta Asample}{\Delta Acontrol}\right) \times 100$$

$\Delta A_{Control} = A_{Control} - A_{Blank}$

$\Delta A_{Sample} = A_{Test\ Sample} - A_{Blank}$

Fifty percent (50%) inhibitory concentration of extract/drug (IC_{50}) was determined using non-linear regression with the aid of statistical package Prism Graphpad® (7.0).

Table 1: List of plants/part used for the study

Plant name	Part used for the study	Date of collection	Voucher number
Ficus capensis Thunb	Leaves	10/05/2021	UIH-23026
Ficus pumila Linn	Whole plant	21/05/2021	UIH-23024
Terminalia catappa Linn	Stem bark	21/05/2021	UIH-23027
Ficus vogelii Miq	Leaves	10/05/2021	UIH-23025
Terminalia mantaly H. Perrier	Stem bark	10/05/2021	UIH-22715
Terminalia ivorensis A. Chev	Leaves	10/05/2021	UIH-23147
Ficus asperifolia Miq	Root	27/05/2021	Not yet allocated
Ficus exasperata vahl	Root	10/05/2021	UIH-23089
Ficus mucuso welw. ex Ficalho	Leaves	21/05/2021	Not yet allocated
Terminalia mollis M.A Lawson	Leaves	02/06/2021	UIH-23020

Alpha Glucosidase Inhibition assay

Alpha glucosidase inhibitory activity of the extracts were established in accordance to a reported method by *Tao et al*. [21] with slight modifications. The assay was carried out in a 96 well microtiter plate. A volume of 20 µL of enzyme solution (0.1unit/mL) prepared in sodium phosphate buffer (0.1M, pH6.9) was added to 20 µL of sample solution prepared in 5% DMSO and 95% sodium phosphate buffer (0.1M, pH6.9) solution. This was pre-incubated at 37 °C for 10 minutes. The reaction was initiated by the addition of 40 µL of PNPG substrate (5 mM) prepared in sodium phosphate buffer and was further incubated at 37 °C for 15 minutes. The reaction was stopped by the addition of 80 µL of 0.2 M Na_2CO_3 prepared in sodium phosphate buffer. Absorbance was read at 405 nm. Assay was carried out in triplicate and the percentage of inhibition was calculated as follows:

$$\%\ inhibition = \left(1 - \frac{\Delta Asample}{\Delta Acontrol}\right) \times 100$$

$\Delta A_{Control} = A_{Control} - A_{Blank}$

$\Delta A_{Sample} = A_{Test\ Sample} - A_{Blank}$

Fifty percent (50%) inhibitory concentration of extract/drug (IC_{50}) was determined using non-linear regression with the aid of statistical package Prism Graphpad® (7.0).

Statistical analysis

All data obtained was expressed as Mean±SEM. One-way analysis of variance (ANOVA) and Tukey's multiple comparison tests was performed to determine the significant differences between values with $P<0.05$. All statistical analysis was performed using Graphpad® (7.0).

Result and Discussion

The methanol extracts of ten *Ficus* and *Terminalia* species were investigated for their inhibitory activities against α-amylase enzyme. It was observed that six (6) plant extracts out of ten showed inhibitions against alpha amylase enzyme in a concentration dependent manner as shown in figure 1 and table 2. This agrees with a study carried out by Imieje *et al*. who reported a concentration-dependent inhibitory effects of the extracts of stem bark of *C.gabunensis* on the activity of α-amylase

enzyme.[22] *Ficus capensis, T. mollis* and *F. vogelli* leave extracts showed significant ($p<0.05$) inhibitory activity with IC_{50} of 343.73±6.13; 344.47±4.66 and 1630.67±2.85 µg/mL, respectively, compared to others. *F. asperifolia root, F. exasperata root, T. mantaly stem bark* and *F. pumila whole plant* extracts showed negative inhibition up to the highest concentration tested (1000 µg/ml) which implies no inhibitory activity. Acarbose showed higher inhibitory activity (74.95% inhibition at 250 µg/mL with IC_{50} 42.20±1.05 µg/mL) as shown in figure 2 compared to the plant extracts investigated.

Methanol extracts of the studied plant species showed inhibition against alpha-glucosidase enzyme across all the extracts in a concentration dependent manner as shown in Table 2. *Terminalia mollis, F. capensis and F. vogelli* leaf extracts showed a significant ($p<0.05$) inhibitory activity with IC_{50} of 6.482±0.61; 11.36±1.01 and 78.47±1.94 µg/mL, respectively, compared with the standard (acarbose) with IC_{50} 2584±9.61 µg/mL.

Alpha amylase and α-glucosidase enzymes are the two major carbohydrate hydrolyzing enzymes targeted in suppressing postprandial hyperglycaemia in type 2 diabetes. Alpha amylase enzyme catalyze the initial step by hydrolyzing α-1,4-glucosidic linkages present in starch and other related polysaccharide into non-reducing sugar while α-glucosidase participate in the final breakdown of non-reducing sugar by the hydrolysis of α-1,4- glycosidic bond into simple sugar (glucose) which is absorbed through the small intestines into the blood stream therefore increasing postprandial blood glucose levels in type 2 diabetes. [15,23] The control of postprandial hyperglycaemia, by slowing down glucose absorption through the inhibition of carbohydrate hydrolyzing enzymes, is one of the therapeutic approaches in managing type 2 diabetes.[24]

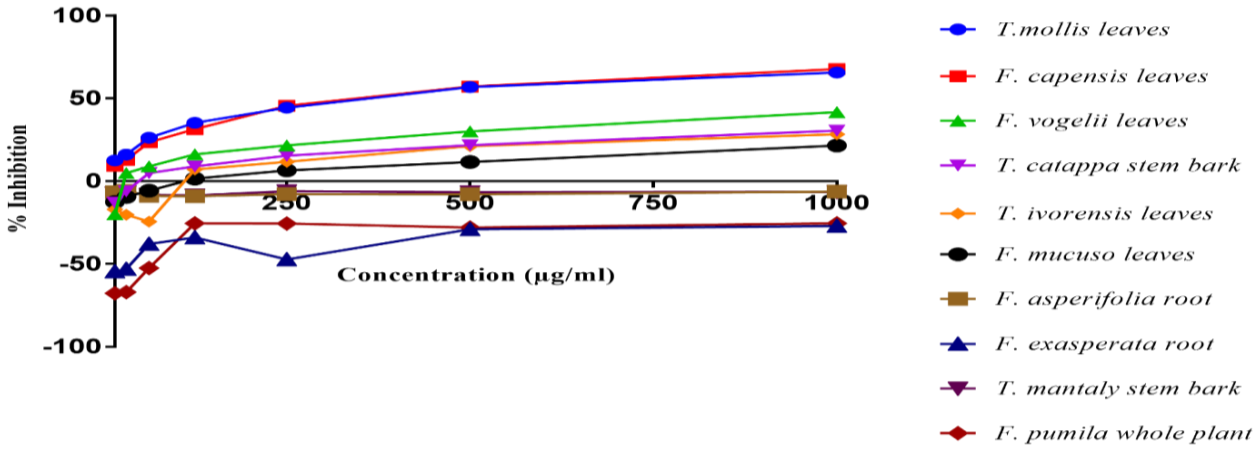

Figure 1: The ten plant extracts showing inhibition against alpha amylase at different concentration

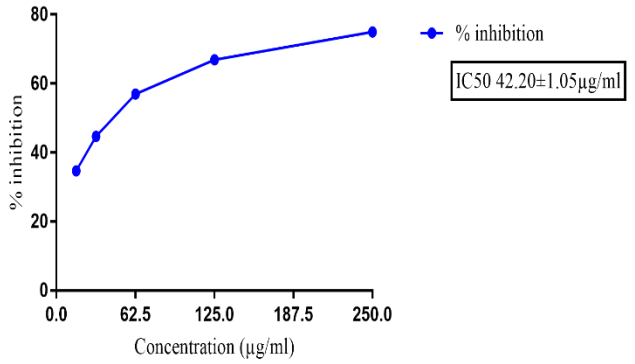

Figure 2: Inhibitory activity of acarbose against alpha amylase enzyme at different concentration

Medicinal plants have been used since ancient times for the management of diabetes. Natural inhibitors from plant source could be an effective therapy for managing postprandial hyperglycaemia with minimal side effects compare to conventional treatments with drugs such as acarbose, voglibose and miglitol.[25] From literature *Ficus* (Moraceae) and *Terminalia* (Combretaceae) are one of those medicinal plants known for their folkloric use for treating several disease conditions including the management of diabetes. [26,27] Ten medicinal plants from genus *Ficus* and *Terminalia* species were selected based on their folkloric usage for diabetes treatment. The investigation of the methanolic extracts of these plant species was carried out for their inhibitory potentials against *α*-glucosidase and *α*-amylase enzymes.

The result of the ten methanol extracts evaluated revealed that *T. mollis* leaf, *F. capensis* leaf, *F. vogelii* leaf, *T. catappa* stem bark, *T. ivorensis* leaf and *F. mucuso* leaf showed inhibitory activity for both porcine pancreatic α-amylase and *saccharomyces cerevisiae* α-glucosidase enzyme. There was a dose-dependent increase in percentage inhibitory activity against α-amylase and α-glucosidase by all the ten plant extracts. This therefore suggest that one of the mechanisms by which these extracts exert their glucose lowering potentials is through the inhibition of *α*-amylase and *α*-glucosidase enzyme. It was also revealed that *F. asperifolia* root, *F. exasperata* root, *T. mantaly* stem bark and *F. pumila* whole plant only showed inhibitory activity for alpha glucosidase enzyme, while these extracts did not show inhibition against α-amylase to an extent that allowed the determination of IC_{50} values. This indicate that the bioactivity of these four extracts exerting inhibitory effect on alpha amylase enzyme, might not be present in sufficient quantity up to the highest tested concentration. The inactivity of these extracts to *α*-amylase enzyme might also be due to the chemical structure of the phytochemicals present in the extracts. This agrees with a study carried out by Kim *et al.* on the inhibition of some flavonoids against α-amylase and *α*-glucosidase enzyme. It was reported by the author that amentoflavone showed strong inhibitory activity against *α*-glucosidase and showed no inhibition for *α*-amylase enzyme which was reported to be due to the positioning of free OH groups present in the compound. [15]

Among plant extracts tested, *T. mollis* and *F. capensis* leaf extracts significantly ($p<0.05$) showed the highest inhibitory activity for both α-amylase (IC_{50}= 344.47±4.66 and 343.73±6.13 µg/mL) and *α*-glucosidase (IC_{50}= 6.482±0.61 and 11.36±1.01 µg/mL) enzymes, respectively. Strong inhibitory activity exhibited by *T. mollis* leaf extract against alpha glucosidase enzyme with IC_{50} 6.482 µg/mL suggests that it contain very promising antidiabetic compounds. This observed bioactivity has shown more prospect compared to some studies that reported high IC_{50} values for *α*-glucosidase inhibitory activity of some extracts. For instance, a study carried out by Shai et al. [28] reported *Cassia abbreviata* as the most active against alpha-glucosidase with IC_{50} of 0.6 mg/mL. In another study carried out by Amiri *et al. Quercus brantii* was reported to inhibit *α*-glucosidase activity with IC_{50} of 7.19mg/mL. [29] Since no anti-diabetic compound has been previously isolated or reported from *T. mollis*, it is therefore plausible that on further investigation to isolate the bioactive

compounds, a new treatment means against type 2 diabetes mellitus (T2DM) may ensue from this plant. Mikailu & Abo , reported glucose lowering activity of *F. capensis* leave extract in Alloxan-Induced diabetic rat which was found to be active. [30] *F. vogelii* leave extract also showed significant inhibitory activity against both enzymes with IC_{50} of 1630.67±2.85 and 78.47±1.94 µg/ml. In general, plant extracts that showed inhibitory activity for both enzymes exerted weak inhibitory activity for porcine pancreatic alpha amylase and strong inhibitory activity for saccharomyces cerevisiae alpha glucosidase. This show agreement with works previously reported that plant phytochemicals exert low inhibitory activity against porcine pancreatic α- amylase and high inhibitory activity against yeast *α*-glucosidase enzymes. [17,31]

Several studies have reported a number of phytochemicals to be responsible for various bioactivities.[32,33] A number of studies identified phytochemicals present in some of the studied plant extracts. For instance, Achi *et al*. reported the presence of tannin, phytates, saponin, alkaloid, terpenoids, flavonoid and phenolics in the leaf extract of *F. capensis*[34]. This study reported the presence of flavonoids, phenolics, steroids, tannins, terpenoid, alkaloids, glycoside, cardiac glycoside, coumarins, steroids and quinones in leaf extract of *T. mollis*. Igile *et al*. [35] reported the presence of flavonoids, polyphenol, steroids, tannins, triterpenoid, alkaloids, glycoside, cardiac glycoside, coumarins, steroids and carotinoid in leaf extract of *F.vogelii*. Rajesh *et al*. [36] also reported the presence of saponin, terpenoid, flavonoid, tannin and phenol in the stem bark of *T. catappa*. A number of studies have shown that some of these phytochemicals are responsible for *α*- glucosidase and *α*-amylase enzyme inhibition. A study carried out by Zhu *et al*. [37] reported a number of flavonoids that showed inhibitory activity for both *α*-glucosidase and *α*-amylase enzymes. Alqahtani *et al*. [38] isolated two triterpenes (3-oxolupenal and katononic acid) from the aerial parts of *N. oppositifolia* which was reported as *α*-glucosidase and *α*-amylase enzymes inhibitors. Rasouli *et al*. screened a number of polyphenols through molecular docking and virtual screening which was reported to have inhibited α-glucosidase and α-amylase enzymes. [39] Coumarins have also been reported to possess inhibitory potential against α-glucosidase and *α*-amylase enzyme. A study carried out by Zhao *et al*. reported a number of coumarins such as edgeworin, daphnoretin and edgeworoside A, isolated from the flowers of *Edgeworthia gardneri* that showed inhibition against α-amylase and *α*-glucosidase enzymes. [40] It is therefore assumed that the inhibitory activity against alpha amylase and alpha glucosidase enzymes exerted by the studied plant extracts could be as a result of the synergistic effect of the phytochemicals present in the extracts. Hence, the results obtained from this study justifies the folkloric use of these plants for the treatment of diabetes.

Table 2: IC_{50} inhibitory effects of the selected plant extracts and standard drug

Sample	*α*-amylase IC_{50} (µg/mL)	*α*-glucosidase IC_{50} (µg/mL)
T. mollis leaves	344.47 ± 4.66	6.482 ± 0.61
F. capensis leaves	343.73 ± 6.13	11.36 ± 1.01
F. vogelii leaves	1630.67 ± 2.85	78.47 ± 1.94
T. catappa stem bark	3087.33 ± 4.26	134.4 ± 4.99
T. ivorensis leaves	3176 ± 15.10	341.7 ± 7.64
F. mucuso leaves	3242.67 ± 22.70	350.67 ± 1.71
F. asperifolia root	-	537.73 ± 1.73
F. exasperata root	-	629.43 ± 0.33
T. mantaly stem bark	-	651.87 ± 3.34
F. pumila whole plant	-	860.9 ± 1.67
Acarbose	42.20 ± 1.05	2584 ± 9.61

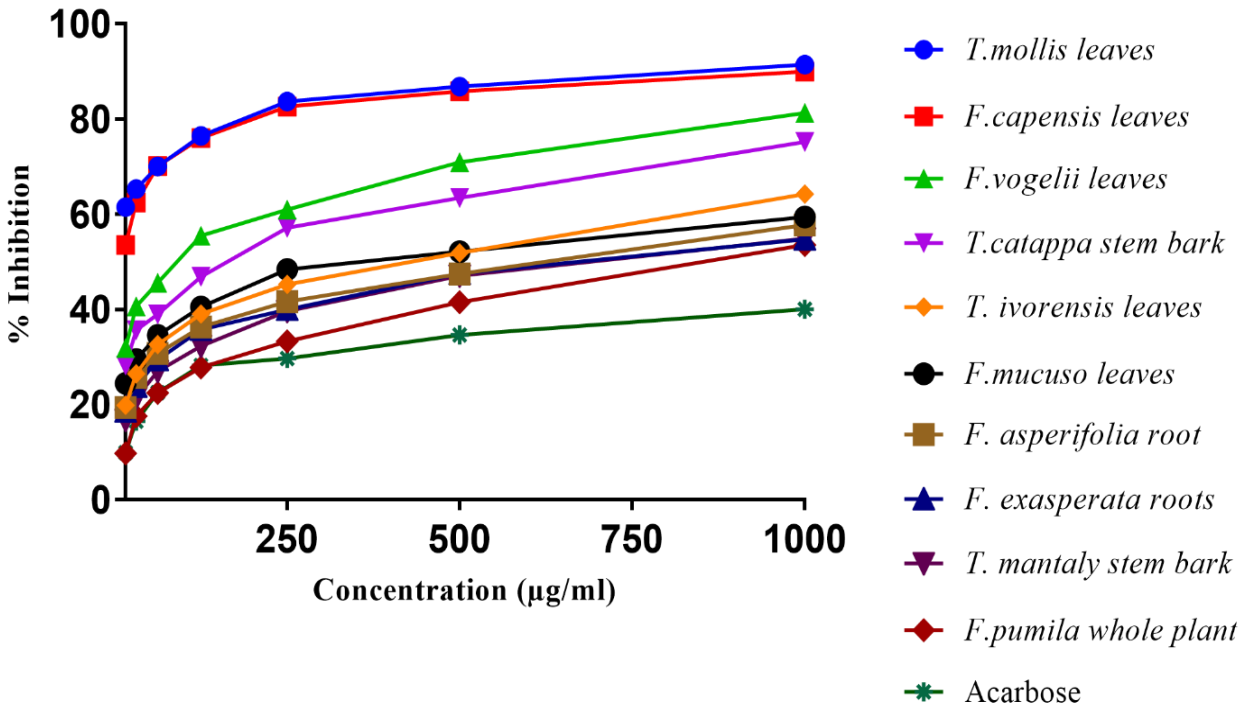

Figure 3: Inhibitory activity of the ten plant extracts and acarbose against alpha glucosidase enzyme at different concentration

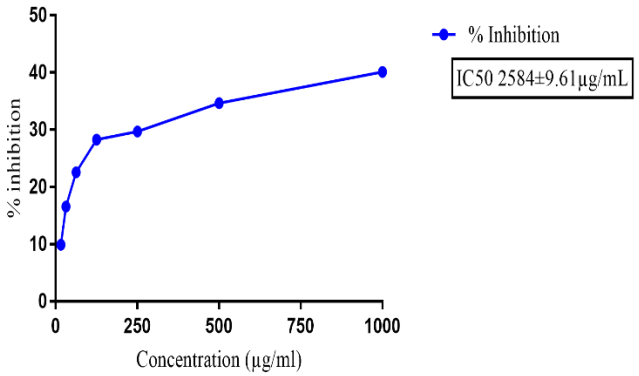

Figure 4: Inhibitory activity of acarbose against alpha glucosidase enzyme at different concentration

Conclusion

The results showed that *Terminalia mollis*, *Ficus capensis*, and *Ficus vogelii* methanolic leaf extracts possess significant inhibitory activity against *α*-amylase and *α*-glucosidase enzymes. These plant extracts showed dose dependent inhibition of the enzymes studied. This justifies their folkloric use for diabetes treatment in traditional medicine.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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