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In vitro Evaluation of the Phytochemical Composition and Kinetics study of *Ficus sur* Leaf Extracts in the Inhibition of *α*-Glucosidase and *α*-Amylase

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ABSTRACT

In Nigerian indigenous medicine, *Ficus sur* finds usage in a wide range of conditions, including diarrhea, anemia, wounds, stomach issues, infertility, peptic ulcers, and gonorrhea. The research aims to evaluate the phytochemical composition and assess the inhibitory capacity of *α*-glucosidase and *α*-amylase leaf extracts of *F. sur*. The leaves of *F. sur* were extracted successively by maceration with acetone, ethanol, methanol, and aqueous. Established methods were adopted to identify the phytochemical and polyphenolic compositions of the herbal extracts; the extracts' *α*-amylase, as well as *α*-glucosidase inhibitory capacity utilizing the Lineweaver-Burke plot to identify mechanisms of inhibition by the enzyme, were further explored. The findings of the phytochemical analysis showed that the liquid extracts of ethanol and methanol contained the greatest quantities of saponin, whereas the extracts of acetone and water had none. Extract from ethanol had a great amount of phenolics (131.86 mg gallic g^{-1}) when compared with methanol (126.12 mg gallic g^{-1}), acetone (92.35 mg gallic g^{-1}), and aqueous extract (48.68 mg gallic g^{-1}). The hypoglycemic results showed that the ethanol extract had much higher inhibition of *α*-glucosidase (IC_{50} = 0.41 mg mL^{-1}) and mild inhibition of *α*-amylase (IC_{50} = 1.39 mg mL^{-1}). According to a Lineweaver-Burk plot analysis, ethanol extract inhibited the two enzymes in non-competitive and competitive ways. *F. sur* leaf extract's high saponins and phenolic content substantiate its hypoglycemic potential.

Keywords: Ethanol extract, *F. sur*, Hypoglycemic, Phenolic acid, Saponin

INTRODUCTION

The defining feature underlying diabetes mellitus (DM) is hyperglycemia, a chronic metabolic illness brought on by anomalies in insulin synthesis, activity, or perhaps both. By 2030, Sub-Saharan areas, including South Africa and Nigeria, were predicted to have a total of 18.6 million such people (Shaw *et al.*, 2010). Even worse Nigeria and South Africa are at the forefront of the ranking of African nations with high frequency, with incidences of 4.5 % percent and 8.30 %, respectively (Federation, 2014). It arises from either the pancreas producing insufficient amounts of insulin or cells in the body failing to respond to the quantity of insulin generated (Shoback & Gardner, 2018). When it comes to DM, there are three primary types of poor tissue response: Type 1 diabetes, which is insulin-dependent diabetes, is more prevalent in young people. The pancreas produces barely any insulin as a result of an autoimmune condition that destroys its beta cells. Frequently referred to as adult-onset diabetes, type 2 diabetes can be brought on by the cells' inability to utilize insulin appropriately. Lastly, gestational diabetes is the term for elevated levels of blood sugar brought on by the liver's insufficient production of insulin in cells while pregnant (Maori *et al.*, 2012).

F. sur is a tropical plant found in tropical and subtropical regions (Saloufou *et al.*, 2018). It is a fast-growing deciduous tree that is sometimes referred to as Petit sycamore or Wild fig (Saloufou *et al.*, 2018). Traditionally, *F. sur* is used in the treatment of boils and snake bites (van Staden & Lall, 2020); its crushed fruits encourage milk during childbirth, while its roots are used to combat female infertility (Saloufou *et al.*, 2018). Scientific information on *F. sur* regarding its compounds and biological activities has been insufficient in the literature, even though some biological activities and compounds have been reported from chromatographic isolation and GC-MS analysis (Ngoh Misse Mouelle *et al.*, 2023; Saloufou *et al.*, 2018). *F. sur* has been implicated as a rich source of polyphenolic compounds (Sieniawska *et al.*, 2022), and plant polyphenols are a possible source of antioxidants. These include phenolic acids, phenols, and flavonoids (Zhou & Ibrahim, 2010). Among the world's most common factors contributing to death are noncommunicable

illnesses, including DM (Baby Joseph & Jini, 2011), which have been linked to the impacts of reactive oxygen species (ROS), aging, civilization, and poor lifestyles (Wild *et al*., 2004). Suppose DM is not managed. In that case, it may result in serious long-term effects, including renal failure, heart disease, foot ulcers, strokes, and eye defects, all of which can be fatal (Jiao *et al*., 2006). This study evaluated the inhibitory properties of *α*-glucosidase and *α*-amylase in *F. sur* leaf extracts for possible application in the control of DM.

MATERIALS AND METHODS

Plant material

In December 2016, *F. sur* leaves were collected in the vicinity of the University of Lagos; herbarium samples were registered (LUH 6936) and placed in the herbarium, Botany Department, Faculty of Sciences, University of Lagos. The plant leaves were pulverized after being air dried for seven days. The pulverized plant sample (100 g) was successively macerated in different batches for 72 hrs. in acetone, ethanol, and methanol, thereafter subjected to decoction at (45–50 ^{o}C) in distilled water. The aqueous extract was freeze-dried, while other extracts were concentrated using a rotary evaporator at 37 ^{o}C. Up to their usage, the extracts were stored at 4 ^{o}C.

Phytochemical Analysis

The qualitative phytochemical analysis of **t**he leaf extracts was ascertained by the techniques previously described in the literature (Asekun *et al*., 2013). While the quantitative phytochemical analysis was conducted according to methods in other literature (Adedapo *et al*., 2009; Nabavi *et al*., 2008). The total flavonoid was calculated by a previously described approach (Samatha *et al*., 2012). Proanthocyanidin was determined using the method in other literature (Sofidiya & Familoni, 2012).

In-vitro Antidiabetic Assay and Kinetic methods

Alpha Glucosidase Inhibition Methods

The inhibitory effect of glucosidase was quantified using the technique described in Sabiu *et al*. (Sabiu *et al*., 2016). The following formula was used to represent the *α*-glucosidase inhibitory impact as a percentage of inhibition:

$$\left[\frac{\Delta\, control\ -\ \Delta\, extract}{\Delta\, control}\right] 100\ =\ \%\, Inhibition$$

The alterations in absorbance for the control and the extracts are represented by ΔA control and ΔA extract, respectively. The concentration that causes 50 % inhibition (IC_{50}) of *α*-glucosidase activities was computed by using a typical calibration curve.

Alpha-Amylase Inhibitory Assay

A test tube containing 250 μL of extract and 250 μL of 0.02 M sodium phosphate buffer (pH 6.9) containing 0.5 mg/mL of *α*-amylase solution was used by the modified method previously described in the literature (McCue & Shetty, 2004). Trials were conducted in triplicate, and the following expression was used to determine the percentage of inhibition for *α*-amylase inhibitory activity: (ΔA control - ΔA extract)/ΔA control = % Inhibition, where ΔA control and ΔA extract, respectively, represent the differences in absorbance from the control and extract samples. The herb extract concentrations that led to a 50 % inhibition of enzyme activity were determined using graphics (IC_{50}).

Mechanism of Inhibitions Alpha-Glucosidase and Alpha-Amylase Inhibition

F. sur extracted from ethanol exhibited the most potent activity from preliminary checks and was used to study the enzyme kinetics for *α*-glucosidase activity inhibition. The modified version of Dnyaneshwar and Archana's (Nagmoti & Juvekar, 2013) methodology was applied. A *p*-nitrophenol typical curve assessed the quantity of lowered sugars released calorimetrically. Following the computation of reaction rates (v), the kind of inhibition was investigated by drawing twin reciprocal graphs showing the kinetics of the enzyme using the conventional Lineweaver and Burk methods. Utilizing the corresponding Lineweaver-Burk graph (1/v against 1/[S]) (Lineweaver & Burk, 1934). Utilizing the modified methodology previously reported in the literature (Ali *et al*., 2006), the process of *α*-amylase inhibition with a particularly potent leaf extract was investigated. To ascertain the inhibitory mechanism, a Lineweaver-Burk twin reciprocal plot (1/v versus 1/[S]) was made, in which [S] stands for substrate concentration and v for response velocity.

Statistical Analysis

A percentage representation of the antioxidant capacity was given. Utilizing GraphPad Prism 5 (the GraphPad program Software, USA), the inhibition of *α*-amylase as well as *α*-glucosidase was calculated, and the phytochemicals that were used were quantified by calculating the mean ± standard deviation (SD). For decisions made in triplicate, the findings were presented in triplicate as mean ± SEM following a one-way analysis of variance (ANOVA) plus a Bonferroni test on the data.

RESULTS

Phytochemical Analysis

The qualitative phytochemical analysis of *F. sur*'s acetone, ethanol, methanol, and water extracts showed the presence of cardiac glycosides, steroids, phenols, terpenoids, tannins, saponins flavonoids, and alkaloids (Table 2) at different concentrations of the extracting solvents. According to Table 2, the results of the quantitative

phytochemical analysis revealed that methanol had the highest phenolic compounds in comparison with the rest of the extracting solvents.

Table 1: Phytochemical Composition of Leave Extracts of *F. sur*

Phytochemicals	Acetone extract	Ethanol extract	Methanol extract	Water extract
Cardiac glycoside	+	+	+	+
Steroids	-	+	++	-
Phenols	++	++	++	+
Terpenoids	-	-	-	-
Tannin	++	++	++	+
Saponin	-	+ +	+	+
Flavonoid	++	++	++	+
Alkaloid	+	+	+	+

Key: ++ = Highly present; + = present; - = not detected

***In-vitro* inhibitory potentials of extracts towards both *α*-glucosidase and *α*-amylase enzymes**

The inhibitory capabilities of *F. sur* extracts towards both *α*-glucosidase and *α*-amylase enzymes are depicted in Figures 1 and 2. All the extracts showed significantly higher inhibition percentages of *α*-glucosidase and *α*-amylase enzymes at all doses compared to acarbose. In the meantime, the inhibitory potential of the ethanol extracts was greater than that of acarbose and that of the other extracts. Table **3** reveals that the ethanol extract demonstrated the most significant activity, with IC_{50} values of 1.39 and 0.41 mg/mL, exhibiting mild inhibitory effects on specific *α*-amylase and *α*-glucosidase.

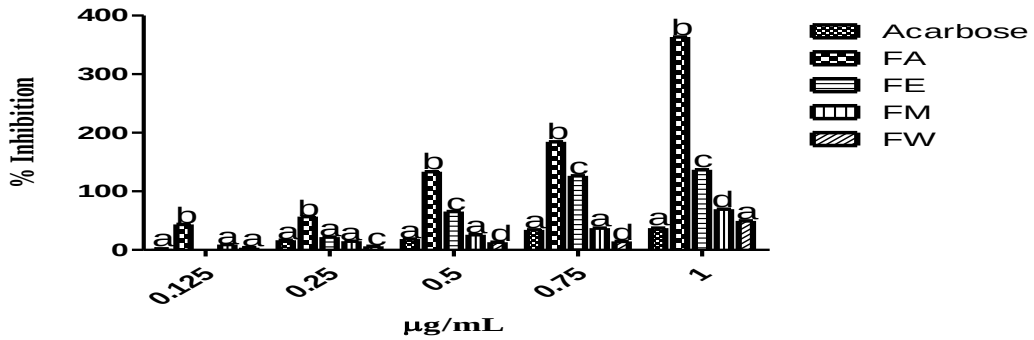

Figure 1: The inhibitory ability of Leaf extracts from *F. sur* towards *α*-glucosidase activity (values represent means ± standard error of triplicate assessments).

Key: FA = *F. sur* acetone extract, FE= *F. sur* ethanol extract, FM= *F. sur* methanol extract, FW= *F. sur* water extract; bars with different amounts that have no plausible letter are significantly distinct ($p < 0.05$)

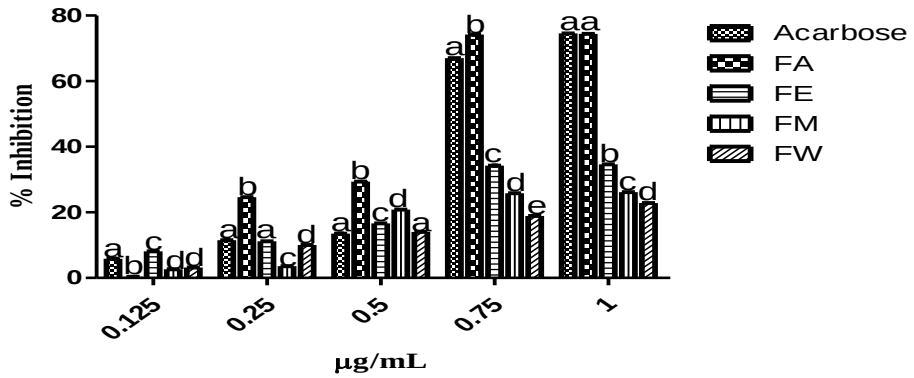

Figure 2: Inhibitory potential of *F. sur* leaf extracts against *α*-amylase activity (values represent means ± standard error of triplicate assessments)

Key: FA = *F. sur* acetone extract, FE= *F. sur* ethanol extract, FM= *F. sur* methanol extract, FW= *F. sur* water extract; bars with different amounts that have no plausible letter are significantly distinct ($p < 0.05$)

Table 2: Total Phenol, Flavonoid, and Proanthocyanidin Composition of Extracts of *F. sur* (mean of triplicate value ± SD)

Phytochemicals	FA	FE	FM	FW
Total Phenols (milligram gallic acid g^{-1})	92.35 ± 0.002	131.86± 0.015	126.12 ± 0.001	48.68± 0.003
Total Flavonoid (milligram quercetin g^{-1})	357.06± 0.001	244.24± 0.002	364.84 ± 0.002	86.40± 0.001
Total Proanthocyanidin (milligram catechin g^{-1})	211.21 ± 001	207.21± 0.001	287.65 ± 0.0015	5.03 ± 0.002

Key: FA = *F. sur* acetone extract, FE= *F. sur* ethanol extract, FM= *F. sur* methanol extract, FW= *F. sur* water extract.

Table 3: IC_{50} values of *α*-amylase and *α*-glucosidase Inhibition of extracts (leaves) of *F. sur*

	IC_{50} (mg/mL)	
Extracts	***α*-amylase**	***α*-glucosidase**
Acarbose	0.71 ± 0.02^{a}	1.28 ± 0.05^{a}
Acetone	0.63 ± 0.01^{b}	0.08 ± 0.01^{b}
Ethanol	1.39 ± 0.05^{c}	0.41 ± 0.03^{c}
Methanol	1.65 ± 0.04^{d}	0.79 ± 0.05^{d}
Water	2.26 ± 0.01^{e}	1.26 ± 0.02^{a}

The mean ± standard error of the mean (n=3) is displayed for each IC50 value determined using the linear regression equation; values exhibiting distinct asterisks in a single column of every parameter indicate statistical significance ($p<0.05$).

The mechanism of inhibition exhibited by the *α*-glucosidase and *α*-amylase enzymes

The mechanisms of consistent inhibition of both forms of *α*-amylase and *α*-glucosidase enzymes were investigated utilizing the Lineweaver-Burk plot. The extracts of ethanol revealed that they were not competitive (Figure 3) and combined non-competitive ways of inhibition accordingly (Figure 4).

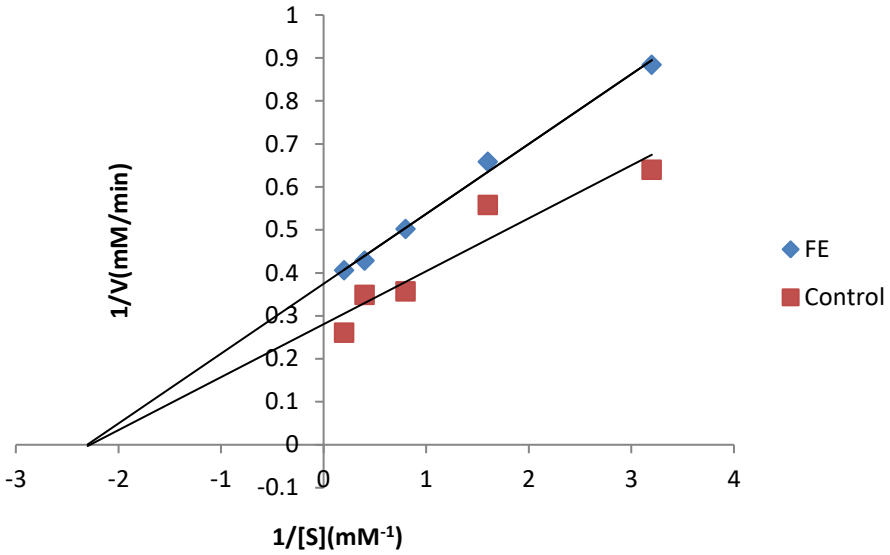

Figure 3: Non-Competitive Mode of *α*-glucosidase Inhibition for FE

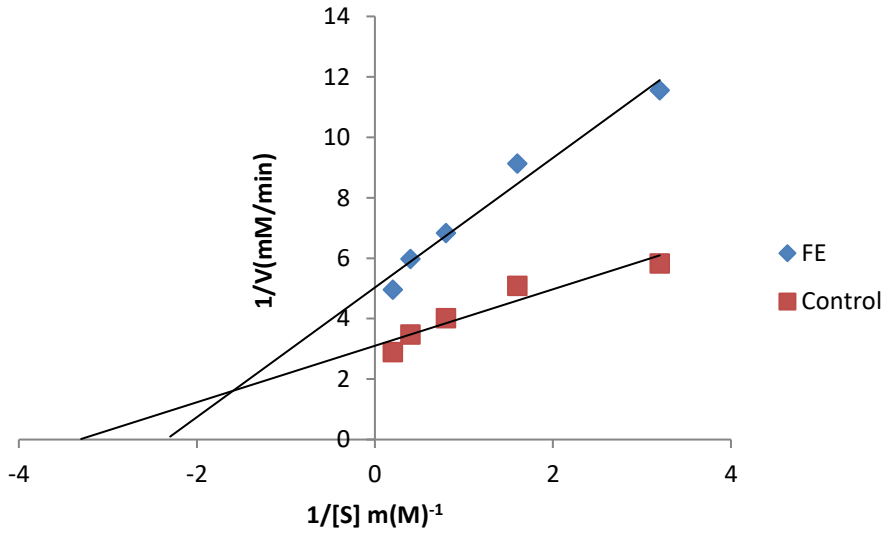

Figure 4: Mixed Non-competitive Mode of Inhibition of *α*-amylase for FE

DISCUSSION

Hyperglycemia, a high blood sugar level that is frequently linked to type II DM, produces an increase in ROS geared towards oxidative stress inside the human body (González *et al*., 2023). Diabetes-related hyperglycemia boosts the generation of free radicals and ROS, which cause membrane-bound macromolecules to autoxidize and start cellular damage (González *et al*., 2023). According to reports, oxidative stress is caused by a discrepancy that exists between the pace at which ROS build up and the protective capabilities of antioxidants, impairing organs (Pizzino *et al*., 2017). Overall, oxidative stress has been shown to worsen the pathophysiology and associated consequences of most illnesses, including DM. Using antioxidants to reduce oxidative stress may be a successful strategy for reducing the difficulties linked with diabetes (Johansen *et al*., 2005). According to the Diabetes Control and Complications Trial (DCCT) (Control & Group, 1993), clinical headaches can be significantly reduced by effective blood glucose regulation. However, even optimal blood glucose regulation

may not prevent complications, indicating the need for non-conventional treatment approaches (Control & Group, 1993). For this reason, this investigation was necessary. According to literature (Sabiu *et al*., 2016), the elevated blood glucose levels found in diabetics were attributed to the uncontrollably high starch hydrolysis by gastrointestinal *α*-glucosidases, which then take up glucose by pancreatic *α*-amylase.

Plant-derived *α*-amylase and *α*-glucosidase that possess exceptional antioxidant capacities are alternatives that should be used. The ethanol extract of *F. sur* leaves (FE) demonstrated an intense inhibitory capacity on *α*-amylase and *α*-glucosidase; this might be employed as a successful means of reducing postprandial hyperglycemia in diabetics. Using plants as a natural remedy for conditions like hyperglycemia has advantages over synthetic equivalents, including synergistic effects, lower cost, and fewer side consequences such as discomfort of the abdomen, tympanites, and likely diarrhea because of the decomposition of unprocessed starches by bacteria in the colon, which are experienced alongside their synthetic counterparts (Atanasov *et al*., 2021). As compared to normal acarbose (1.27 mg/mL and 0.70 mg/mL, respectively), the results of this investigation demonstrated that ethanol extract displayed effective inhibition toward *α*-glucosidase (IC50 = 0.41 mg mL^{-1}) and modest inhibition of *α*-amylase (IC_{50} = 1.39 mg mL^{-1}). For this reason, the extract could be helpful in the creation of nutraceuticals as well as in the treatment of diabetes. The outcomes were consistent with findings by Familoni *et al*. (Familoni *et al*., 2019) and Kwon *et al*. (Kwon *et al*., 2008), which showed that strong *α*-glucosidase inhibitory activity together with mild *α*-amylase inhibition showed an improved curative strategy in preventing the alimentary canal from providing enough dietary carbohydrate substrate for glucose synthesis. The inhibition process was evaluated using the Lineweaver-Burk plot, and it was found that FE reduced the activity of *α*-amylase in a mixed non-competitive manner and *α*-glucosidase in an entirely non-competitive manner. Since FE is non-competitive with *α*-glucosidase, its extract likely binds to an alternative site (the allosteric site), which reduces the enzyme's effectiveness and influences the enzyme's ability to convert substrates into products. According to Kazeem *et al*. (Kazeem *et al*., 2013), a combined-non-competitive function of FE on *α*-amylase could be that the extract binds to both the complex of the enzyme-substrate and the unbound enzyme, exerting an important influence upon the catalytic activity and substrate attraction of the enzyme. This prevents the breakdown of disaccharides into monosaccharides.

ROS have been connected to the etiology found in DM and have the ability to initiate several detrimental pathways that are responsible for both micro- and macrovascular problems in the disease. According to Johansen *et al*. (Johansen *et al*., 2005) and Modak *et al*. (Modak *et al*., 2007), this involves speeding up the production of the end products of advanced glycation (AGE), the polyol pathway, and the hexosamine pathway, including protein kinase C signaling (PKC). The investigation's findings demonstrated a relationship between FE's reported hypoglycemic qualities, phytochemical compositions, and polyphenolic levels. The hydroxyl group's presence affects polyphenolics' capacity for scavenging. Natural antioxidants (polyphenols) reduce ROS activity. These are necessary components that protect people from many forms of cellular harm (Jing *et al*., 2010; Shukla *et al*., 2009). Flavonoids are the most abundant and varied class of vital bioactive phenolics (Table 1) in *Fiscu sur*. By scavenging ROS, they demonstrate antioxidant activity and stop free radical damage. They have beneficial biochemical effects on several diseases, which include cardiovascular diseases, atherosclerosis, and diabetes. Proanthocyanidin significantly lowers (in type 2 diabetic mice) blood sugar and significantly lowers renal age and urine protein (Yokozawa *et al*., 2012). The recorded biological potentials (including hepatoprotective, anti-bacterial, anti-inflammatory, and anticancer properties) of saponins have drawn attention from researchers; it was documented that saponin, from *Holothuria thomasi* (sea cucumber), displayed a substantial hypoglycemic potential since it stimulates insulin action, *β*-cell reformation, as well as the use of glucose enzyme activation in STZ-diabetic rats (Mazumder *et al*., 2023).

CONCLUSION

The phytochemical analysis revealed that ethanol and methanol extracts contained the most saponin, while acetone and water extracts had none. Ethanol extract had the highest phenolic content and higher inhibition of *α*-glucosidase and *α*-amylase enzymes, according to a Lineweaver-Burk plot analysis. The phytochemical makeup of the ethanol extract of *F. sur*, which coincides with its reported antioxidant capabilities, may be responsible for its hypoglycemic potential.

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