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Original Research Article

AQUEOUS AND METHANOLIC EXTRACTS OF SANDPAPER (*Ficus exasperata*) LEAVES: DIABETIC AND ANTIOXIDANT INDICES

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ABSTRACT

Although *Ficus exasperata* is frequently used in traditional medicine to treat oxidative stress-related diseases and diabetes, the biological foundation for its therapeutic actions is still unclear. This study examined the bioactive constituent of methanolic and aqueous leaf extracts of *Ficus exasperata* and evaluated their antioxidant and antidiabetic properties. The chemical constituents of the plant extracts were analyzed through gas chromatography–mass spectrometry (GC–MS). The inhibitory activities against α-amylase and α-glucosidase were assessed using established in vitro enzymatic assays, while the antioxidant properties were evaluated through DPPH, ABTS, FRAP, hydrogen peroxide (H_2O_2), and SOD-mimetic radical scavenging assays, employing acarbose as the reference standard. GC-MS result showed that aqueous extract of *Ficus exasperata* contained 29 phytochemicals, dominated by phenol, 2-methoxy- (19.66%), phytol (12.12%), estra-1,3,5(10)-trien-17β-ol (8.14%), and 1,2,3,4-tetrahydroisoquinolin-6-ol-1-carboxylic acid (7.59%). The methanolic extract yielded 12 compounds, with phytol (28.83%), squalene (11.47%), hexadecanoic acid methyl ester (10.88%), and 9,12-octadecadienoic acid methyl ester (8.42%) as major constituents. Both extracts demonstrated concentration-dependent α-amylase and α-glucosidase inhibition, with aqueous extract showing stronger α-amylase inhibition (IC_{50} = 41.19 µg/mL) than the methanolic extract (IC_{50} = 61.43 µg/mL), whereas methanolic extract exhibited a slightly greater α-glucosidase inhibition (IC_{50} = 47.68 µg/mL) compared to aqueous extract (IC_{50} 47.78µg/mL). Antioxidant analysis revealed dose-responsive radical scavenging activity in both extracts, with the aqueous extract showing higher DPPH, ABTS and FRAP activity while methanolic extract exhibited greater H_2O_2 and SOD-like activities. The presence of phytol, squalene, phenolic derivatives, fatty acid esters, and terpenoids supports the pharmacological relevance of *F. exasperata* as a hypoglycemic and antioxidant agent. The findings validate its traditional use in diabetes management and highlight its potential for development into safer, plant-based therapeutic formulations.

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INTRODUCTION

Diabetes mellitus (DM) remains a significant public health concern, characterized by its complex metabolic nature and its growing impact as one of the most enduring and pressing health issues worldwide [1]. Over 463 million people worldwide suffer from its worldwide, and by 2045**, that number is expected** to rise to 700 million, with an estimated 6.7 million deaths globally [2]. It has been associated with lots of diseases including peripheral vascular disease, cerebrovascular illness, cardiovascular disorders, retinopathy, nephropathy, and neuropathy [3,4]. Type 2

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diabetes mellitus (T2DM) is a multifactorial chronic metabolic disorder characterized by accumulated glucose in the blood, primarily arising as a result of defects in insulin receptors and/or pancreatic β-cell dysfunction leading to inadequate insulin secretion [5]. Under normal physiological conditions, dietary carbohydrates are enzymatically degraded into monosaccharides such as glucose, which serve as the principal energy substrate for cellular metabolism [6]. Following digestion, glucose is absorbed across the intestinal epithelium into the circulation, triggering pancreatic insulin release. The secreted insulin facilitates glucose uptake by skeletal muscle and adipose tissue for metabolic energy generation, thereby promoting hepatic glycogen synthesis for glucose storage [7].

In Type 2 Diabetes Mellitus (T2DM), the normal coordination of glucose regulation becomes severely disrupted. The insulin sensitivity of peripheral tissues declines, while the pancreatic β-cells fail to produce an adequate compensatory amount of insulin [7]. The process of carbohydrate digestion is governed by two essential hydrolytic enzymes (α-amylase and α-glucosidase), which are critical for maintaining postprandial glucose balance. The enzyme α-amylase (EC 3.2.1.1) initiates the cleavage of α-1,4-glycosidic bonds in starch, maltodextrins, and maltooligosaccharides, beginning the degradation of complex carbohydrates mainly in the salivary glands and the pancreas [8–10]. Salivary α-amylase begins the process of starch degradation in the oral cavity, whereas pancreatic α-amylase is secreted into the duodenum to continue the digestion of ingested starch [11]. α-α-Glucosidase (EC 3.2.1.20) is a multifactorial exohydrolase that cleaves glucose units from the non-reducing ends of oligosaccharide substrates, thereby facilitating the final release of absorbable glucose [12,13].

Inhibiting the activity of these two digestive enzymes helps slow down how quickly glucose enters the bloodstream after eating carbohydrate-rich foods. This delay in glucose absorption helps prevent an instant rise in blood sugar levels after meals and serves as an effective and safe approach for managing Type 2 Diabetes Mellitus (T2DM), and conditions involving reduced glucose tolerance [9,14]. Drugs such as Acarbose, Miglitol, and Voglibose are standard pharmacological inhibitors of the digestive enzymes α-glucosidase and α-amylase, which work by blocking these enzymes in the intestine and pancreas, thereby slowing down the breakdown of carbohydrates and reducing the rate at which glucose is absorbed into the bloodstream [15]. Although effective, these drugs have been associated with gastrointestinal adverse effects, including flatulence, bloating and diarrhoea, which arise from the fermentation of undigested carbohydrates by colonic microbes [15].

Oxidative stress is a key factor that contributes in the development and progression of Type 2 Diabetes Mellitus. It occurs when the body produces more reactive oxygen species (ROS) than its antioxidant system can effectively neutralize [16,17]. Under physiological conditions, ROS such as superoxide anions (O_2^-), hydroxyl radicals (OH), and hydrogen peroxide (H_2O_2) are naturally produced during mitochondrial oxidative phosphorylation and function in redox signaling, immune regulation, and cellular homeostasis [18]. However, persistent hyperglycemia in T2DM enhances ROS production via glucose autoxidation, protein glycation, and activation of the polyol pathway [19,20]. Auto-oxidation of glucose leads to free radical formation, while non-enzymatic glycation generates advanced glycation end-products (AGEs) that amplify oxidative injury [21]. Increased flux through the polyol pathway depletes Nicotinamide Adenine Dinucleotide Phosphate (NADPH), thereby limiting glutathione (GSH) regeneration and weakening antioxidant defense mechanisms [22]. The resulting oxidative damage to lipids, proteins, and nucleic acids contributes to β-cell dysfunction, insulin resistance, and microvascular and macrovascular complications of diabetes[19,23]. Although the body has its own defenses to remove harmful free radicals, these protective systems weaken as we age or when the body is exposed to stress. When this happens, excess reactive oxygen species (ROS) begin to damage cells and disrupt normal metabolism [24,25]. This has implicated free radicals as a major causative factor in the development of many diseases, including heart conditions, diabetes, arthritis, cancer, liver problems, aging-related disorders, and even immune system illnesses like HIV/AIDS [26,27].

Quantification of total antioxidant activity (TAA) is routinely performed using antibody-based, fluorescence, luminescence, spectrophotometric, chromatographic, and electrophoretic methods [28]. Among these, spectrophotometric assays are preferred due to their simplicity, reproducibility, and cost-effectiveness [29,30]. Commonly applied

colorimetric methods include the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay, which evaluates hydrogen-donating capacity[28]; the 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate) (ABTS) assay, which measures total antioxidant potential through the decolorization of $ABTS^{+}$ radicals [31,32]; and the Ferric Reducing Antioxidant Power (FRAP) assay, which assesses the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) ions [33]. Other radical scavenging tests, including hydroxyl and superoxide assays, determine the ability of samples to neutralize specific reactive intermediates implicated in oxidative stress–mediated diabetic complications [34].

Ficus exasperata Vahl (family: Moraceae), commonly known as the sandpaper tree or sandpaper leaf, is a perennial medicinal plant widely distributed across tropical Africa and parts of Asia. Taxonomically, it belongs to the genus Ficus, which encompasses over 800 species known for their rich phytochemical and therapeutic profiles [35]. The plant is characterized by rough, sandpaper-like leaves, a milky latex, and small syconium fruits typical of the genus. *F. exasperata* thrives in humid and semi-deciduous forest zones and is commonly found growing along roadsides, riverbanks, and secondary forests [36]. Phytochemical investigations have revealed that the plant is rich in phenolic compounds, flavonoids, tannins, alkaloids, and saponins, which collectively contribute to its biological activities [15,37]. Several studies have been carried out on the use of *F. exasperata* leaves, bark, and latex for the management of diabetes mellitus [15,38–41], treatment of infection [42], hypertension / diuretic effect [43], wounds [44], and various inflammatory conditions [45]. Ajao *et al*., [41] reported that aqueous extracts of *F. exasperata* significantly reduced blood glucose levels and oxidative stress biomarkers in streptozotocin-induced diabetic rats. Mouho *et al*., [46] evaluated *F. exasperate, and reported* 31 phenolic compounds from the leaves and barks of *F. exasperate*, and found strong DPPH, NO, and superoxide radical scavenging but weak α-amylase inhibition, confirming antioxidant potential. Woode *et al*., [47] showed that ethanolic extract of *F. exasperate* leaf exhibited dose-dependent antioxidant and anti-arthritic effects. Jimoh-Abdulghaffaar *et al*. [48] demonstrated that aqueous extract reversed diabetic neuropathy and oxidative stress, enhancing SOD and GSH levels. Despite the breadth of work, important gaps remain, as majority of previous studies either emphasize in vivo glycaemic and organ-protective outcomes. Therefore, in this study, we examined the chemical compounds, hypoglycemic and antioxidant activity of aqueous and methanolic extracts of *Ficus exasperata* (sandpaper leaf), with the aim to identify the bioactive constituents responsible for its use in treatment and management of metabolic disorders.

MATERIALS AND METHODS

Plant Collection

Fresh leaves of *Ficus exasperata* were obtained from the agricultural field of the Federal University of Technology, Owerri (FUTO), Nigeria. The specimen was taxonomically authenticated by Prof. I. Duru from the Department of Biological Sciences, FUTO, and a voucher specimen was preserved for reference. A voucher specimen was deposited in the departmental herbarium under voucher number FUTO/BIO/2024/032.

Chemicals, Drugs and Equipment

All analytical-grade chemicals and reagents used in this study were procured from Sigma–Aldrich (St. Louis, MO, USA). These included methanol, sodium phosphate, p-nitrophenyl-α-D-glucopyranoside (pNPG), Acarbose, Baker's yeast, ABTS, TPTZ, sodium acetate trihydrate, riboflavin, Griess reagent, ferric chloride, thiobarbituric acid (TBA), DPPH, ascorbic acid, phenanthroline, and ferrous sulfate. Deionized water was supplied by the Department of Chemical Engineering, FUTO.

Extraction of *Ficus exasperata* leaves

The leaves were rinsed under running water and then left to air dry in the shade for three weeks at room temperature. The dried leaves were pulverized into a fine powder using an electric blender. For seven days, 195g of the powdered material was macerated separately in 500mL of methanol and distilled water, with periodic stirring. To eliminate any remaining solvents, the filtrates were concentrated in a water bath maintained at 60 degrees Celsius. Before analysis, the resultant crude extracts were kept between 0 and 4°C. Equation (1) was used to calculate each extract's extraction yield.

$$\text{Percentage yield (\%)} = \frac{Q}{W} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where Q refers to the quantity (mass) of the extracted, W represents the initial weight (mass) of the raw material.

Treatment Design

Adult Wistar rats were randomly assigned into three experimental groups (n = 3 per group): Group I (Control) received distilled water; Group II received aqueous extract of *Ficus exasperata* leaves at a dose of 400 mg/kg body weight; and Group III received methanolic extract of *Ficus exasperata* leaves at a dose of 400 mg/kg body weight. The extracts were administered orally by gavage once daily for 14 consecutive days. At the end of the treatment period, blood samples were collected under standard laboratory conditions and used for subsequent *in vitro* antidiabetic and antioxidant analysis.

GC-MS analysis of *Ficus exasperata* leaf extract

According to the method used in Hossen *et al*. [49], the bioactive components of the aqueous–methanolic extract were examined using Gas Chromatography–Mass Spectrometry (GC–MS) on a PerkinElmer Clarus 500 apparatus equipped with an Elite-1 fused silica capillary column (30 m × 0.25 mm × 0.25 µm; 5% phenyl methyl siloxane). The mobile phase was 99.99% pure helium gas that was maintained at a constant flow rate of 1.5 mL/min. With the injector and ion source temperatures set at 300 °C and 250 °C, respectively, a 1 µL aliquot of the extract was added in split mode (50:1). The oven temperature program started at 35 °C and was maintained for 5mins. It then gradually increased to 150 °C at a rate of 4 °C per minute, 250 °C at a rate of 20 °C per minute, and 300 °C for an additional five minutes. At an ionization energy of 70 eV, the mass spectra were obtained in the 45–450 Da m/z region. By comparing the acquired spectra with reference information from the National Institute of Standards and Technology (NIST) database, chemical substances were identified [50].

Determination of alpha amylase inhibitor activity of *Ficus exasperata* leaf

The α-amylase inhibitory activity was determined following the procedure described by [15] with minor modifications. In this assay, 200 µL of 0.02 M sodium phosphate buffer (pH 6.9) was mixed thoroughly with 20 µL of α-amylase enzyme solution, after which varying concentrations of the plant extract (50, 100, 150, 200, and 250 µg/mL) were introduced. The resulting mixture was allowed to incubate at ambient temperature for 10 minutes to facilitate enzyme–substrate interaction. The reaction was initiated by the addition of 200 µL of soluble starch solution as substrate, followed by 400 µL of 3,5-dinitrosalicylic acid (DNS) reagent to terminate the enzymatic process after heating for five minutes and subsequent cooling. The reaction mixtures were then diluted with 15 mL of distilled water before measurement. A reaction mixture containing all reagents except the extract served as the control, representing 100% enzyme activity. The absorbance of the resulting solutions was measured at 545 nm to assess the degree of enzyme inhibition. The % inhibition was calculated using equation (2)

$$\propto -amylase\ inhibition\ (\%) = \frac{A_{540c} - A_{540s}}{A_{540c}}\ x\ 100\% \quad \text{.....(2)}$$

The half-maximal inhibitory concentration (IC_{50}) was calculated from the plot of inhibition percentage against log inhibitor concentration. Acarbose served as a positive control.

Determination of alpha glucosidase inhibitor activity

Using p-nitrophenyl-α-D-glucopyranoside (pNPG) as the substrate, the α-glucosidase inhibition was measured in accordance with the method of [15]. 100 mM phosphate buffer (pH 6.8) was used to create the enzyme solution. The substrate (pNPG) was added after mixture of extract at different concentrations (50, 100, 150, 200, and 250 µg/mL) with 320µL of buffer and pre-incubated at 30°C for five minutes. Absorbance was measured at 410 nm after the reaction was stopped with 3mL of 50mM NaOH. Every experiment was carried out in triplicate using acarbose as the standard inhibitor. The % inhibition was calculated using equation (3)

$$\propto -glucosidase\ inhibition\ (\%) = \frac{A_c - A_s}{A_c}\ x\ 100\% \quad \text{.....(3)}$$

where Ac is the absorbance of the control and As is the absorbance of the sample.

1, 1, diphenyl 2-picryl hydrazyl (DPPH) Radical Assay

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay was used to assess the antioxidant capacity of the aqueous-methanolic extract of Ficus exasperata leaves as reported in [51] . 1.0 mL of the extract at varying concentrations (10, 20, 30, 40, and 50 µg/mL) was combined with 4.0 mL of a 0.1 mM DPPH solution made in methanol. After 30 minutes of dark incubation at room temperature, the reaction mixture was evaluated for absorbance at 517nm using a UV-visible spectrophotometer in comparison

to a methanol blank. The scavenging effect was determined using Equation (3):

$$I_{DPPH}\ (\%) = \left(\frac{A_b - A_s}{A_b}\right) x100 \quad \text{.....(4)}$$

Where A_b and A_s represent the absorbance of the control.

2, 2-Azinobis (3-ethylbenzo-thiazoline-6-sulfonate (ABTS) radical scavenging ability

To achieve full radical production, a solution containing 7 mM ABTS and 2.45 mM potassium persulfate was reacted and allowed to incubated at room temperature in a light-restricted environment for around 16 hours as reported in [52]. After that, the $ABTS^+$ solution was diluted with distilled water until it reached an absorbance value of 0.70 ± 0.02 at 734 nm. For the antioxidant test, 2.0 mL of the standardized $ABTS^+$ working solution was combined with 0.2 mL of the plant extract at different doses (10–50 µg/mL). A 15-minute reaction time at room temperature was observed prior to measurement. Using a UV–V spectrophotometer and distilled water as the blank, the absorbance drop was measured at 734 nm. The percentage inhibition of $ABTS^+$ radicals was calculated using Equation (5):

$$I_{ABTS^+} = \frac{A_c - A_s}{A_c} x100 \quad \text{.....(5)}$$

A_c is the absorbance of ABTS+ in methanol and A_s is the absorbance of ABTS+ in plant extract.

Ferric reducing antioxidant power assay (FRAP)

Ferric reducing antioxidant power (FRAP) was quantified following the procedure described by [53]. A 300mM acetate buffer (pH 3.8), 10mM TPTZ prepared in 40mM HCl, and 20mM $FeCl_3 \cdot 6H_2O$ were combined in a volumetric ratio of 10:1:1 to create the FRAP working reagent. The reagent mixture was equilibrated at 37 °C, and 3.6 mL of the preheated FRAP reagent was mixed with 80 µL of the plant extract (100 µg/mL), and the mixture was left to react for 10 minutes at a regulated temperature. At 593 nm, the absorbance of the resultant chromogenic complex was then determined. The FRAP scavenging ability of the extract was calculated using Equation (6).

$$FRAP\ (\%) = \left(\frac{A_s - A_b}{A_b}\right) x100 \text{.....(6)}$$

A_s= absorbance of the reaction mixture containing the extract, A_b = absorbance of the blank

Hydroxyl Radical Scavenging Assay

The hydroxyl radical scavenging potential of the extract was evaluated using a modified procedure adapted from [53]. In this assay, 80 µL of the extract (100 µg/mL) was combined with 1.0 mL of 1,10-phenanthroline (0.75 mM), 2.0 mL of sodium phosphate buffer (0.2 M, pH 7.4), and 1.0 mL of $FeSO_4$ solution (0.75 mM). The reaction was initiated by introducing 1.0 mL of hydrogen peroxide (0.01%), after which the mixture was incubated at 37 °C for 30 minutes. The absorbance of the final solution was recorded at 536 nm against a reagent blank, and the percentage hydroxyl radical scavenging activity was computed using the corresponding equation (7):

$$I_{OH^-}(\%) = \frac{(A_s - A_b)}{A_w - A_b} x100 \text{.....(7)}$$

where A_w, A_b, and A_s is the absorbance of the deionized water instead of H_2O_2, ascorbic acid and extract, respectively.

Superoxide Anion Scavenging Activity

The superoxide anion scavenging capacity of the extract was determined following the riboflavin–NBT photoreduction technique, as reported in hussen[53] with slight modifications. The reaction system (3.0 mL total volume) comprised 50 mM phosphate buffer (pH 7.6), 17.7 µM riboflavin, 12 mM EDTA, 0.1 mg nitroblue tetrazolium (NBT), and 2.18 mM sodium cyanide. To this mixture, 80 µL of the plant extract (100 µg/mL) were introduced, and the preparation was then exposed to fluorescent light for 15 minutes at ambient temperature to initiate the photochemical reaction. The formation of formazan was quantified by reading the absorbance at 560 nm, and the percentage inhibition of superoxide radicals was computed based on the control reaction and calculated based on equation (8).

$$I_{O^{2-}}(\%) = \left(\frac{A_b - A_s}{A_b}\right) x100 \quad (8)$$

A_b is the absorbance of the control reaction (without extract) and $A_s$is the absorbance in the presence of the plant extract.

Ethical Approval Statement

Ethical approval for this research was granted by the Research and Ethics Committee of the Department of Biomedical Engineering, Federal University of Technology, Owerri (FUTO) during its 29th meeting held on April 27, 2025 (Ref No: FUT/SEET/BME/pgsp-03/Vol. 9). All experimental procedures were performed in strict compliance with the institutional and regulatory ethical guidelines governing research.

Statistical Analysis

All results were expressed in bar-chart, with each assay performed in triplicate. The data obtained from the experiments were subjected to a paired sample *t*-test statistical evaluation using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA), to determine which extract performed better.

RESULTS

Yield of the extracts

Result of the yield of aqueous and methanolic extract of *F. exasperata* leaves after extraction showed that methanolic extract had a higher yield (24.21%) compared to the aqueous extract (23.52%) as showed Table 1.

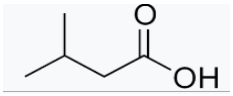
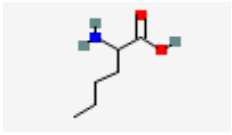
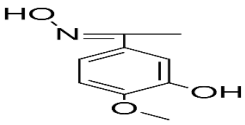
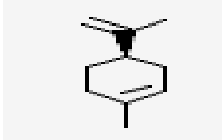
Table 1: Percentage yield of crude extract

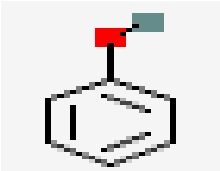
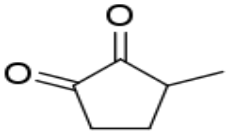
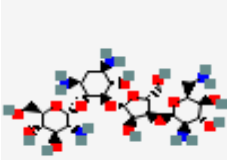
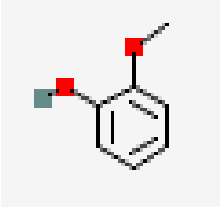
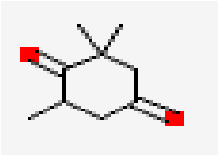
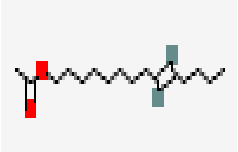
Solvent	Weight of the crude extract (g)	Percentage Yield (%)
Aqueous extract	45.86	23.52
Methanolic extract	47.21	24.21
Total Yield	93.07	47.73

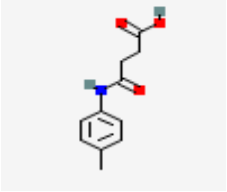
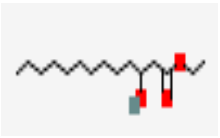
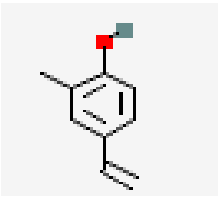
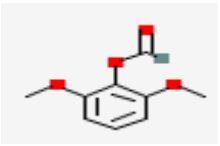
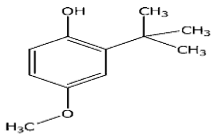
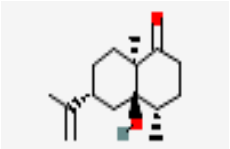
GC-MS Analysis of Aqueous and Methanolic Extract of *F. exasperata*

The GC–MS analysis of the aqueous extract of Ficus exasperata leaves revealed twenty-nine (29) bioactive compounds with diverse chemical classes including phenolics, fatty acids, terpenoids, and esters (Table 2). The most abundant compounds identified were phenol, 2-methoxy- (19.66%), phytol (12.12%), estra-1,2,5(10)-trien-17β-ol (8.14%), 1,2,3,4-tetrahydroisoquinolin-6-ol-1-carboxylic acid (7.59%), and 2-methyl-4-vinylphenol (7.12%). These compounds accounted for over half of the total area percentage, indicating their dominance in the extract's phytochemical composition. The methanolic extract of *F. exasperata* leaves yielded twelve (12) major phytochemical compounds (Table 3). The most abundant were phytol (28.83%), squalene (11.47%), hexadecanoic acid methyl ester (palmitic acid methyl ester, 10.88%), and 9,12-octadecadienoic acid methyl ester (8.42%). These compounds accounted for over 59% of the total chromatographic area, suggesting that they are the primary contributors to the extract's biological activity.

Table 2: Bioactive chemical constituent of aqueous extract of *F. exasperata* leaves

S/N	Names of the compound	RT (mins)	Area %	Chemical structure	Medicinal use	Reference
1.	3-methylbutanoic acid	7.836	0.87		Anti-tumour therapy. Anticonvulsant agent.	[54]
2.	dl- norleucine	8.096	2.27		Anti-neurotoxic effect of alzheimer's disease	[55]
3.	Oxime, methoxy-phenyl-,	9.321	0.63		It is used as anti-dote for nerve agents that reactivate acetylcholinesterase	[56]
4.	R- limonene	9.321	1.14		It is used for the relieve gallstones, gastroesophageal reflux disease, and heartburn.	[57]
5.	Dodecanioc acid, 3-hydroxyl-	10.978	1.12		It is used in treatment for acne	[58]

6.	Phenol	11.748	5.13		It is used as an antioxidant	[59]
7.	Cyclopentanedione, 3- methyl	12.722	3.01		It has been reported as an antioxidant.	[60]
8.	Paromomycin	14.317	0.69		It is an antibiotic used in treatment of infections such as amebiasis, tapeworm infection	[61,62]
9.	Phenol, 2-methoxy	14.615	19.66		It is used for treatment of bacterial infection, cardioprotective effect, antioxidant and also use for anti-inflammation.	[63–65]
10.	17-octadecynoic acid	16.053	1.57		It is used in the antihypertensive agent, and associated in inflammation	[66]
11.	2,6-nonadienoic acid, 7- ethyl-9-(3-ethyl-3-methyloxiranyl 1)-3- methyl-, methyl- ester, [2r-[2a(2E,6E), 3a)]	17.051	0.89		It is reported for exhibited antioxidant/antimicrobial/cytotoxic activity.	[67]
12.	1,4-cyclohexanedione, 2,2,6 trimethyl-	17.514	1.94		It has been used to block ω-hydroxylation of fatty acids and ischemia/reperfusion injury	[68,69]
13.	9-tetradecen-1-o1, acetate, (E)-	20.028	3.56		It has been reported for its anti-inflammatory and antibacterial properties	[70–72]

14.	Ethanol, 2- (9-octadecenyloxy) -, (Z)-	20.358	1.02		It has been reported for its antifungal and anticancer activities.	[73]
15.	4-oxo-4- (para-tolyl)-butyric acid	20.491	0.89		It is an anti-tumor agent.	[74]
16.	Tridecanioc acid, 3-hydroxy-,ethyl ester	22.102	1.40		It is used for cosmetic as an ingredient	[75]
17.	2- methyl-4-vinylphenol	22.612	7.12		It is an important constituent used for coffee and also a flavouring agent.	[76]
18.	Formic acid, 2,6-dimethoxyphenyl ester.	23.908	2.93		It is an antibacterial agent or substance used in treatment of pest.	[77]
19.	N-(1-hydroxy-4-oxo-1-phenylperhydroquinolizin-3-yl) carbonic acid, benzyl ester	25.613	2.38		It is reported as an antimalaria agent.	[78]
20.	2,2,6,7-tetramethyl-10-oxatricyclo(4.3.1.0(1,6)] decan-5-o1	27.852	1.43			
21.	3-tert-butyl-4-hy-droxyanisole	30.420	1.93		It is an antioxidant stabilizer of fats. It is also used as a food additive.	[79]
22.	Corymbolone	32.141	1.42		It is used in traditional medicine to treat many diseases.	[80,81]

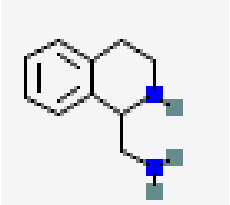
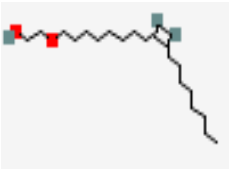
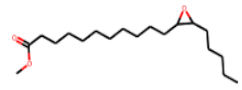
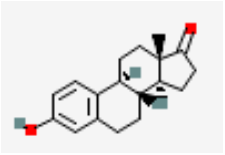
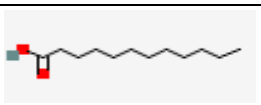
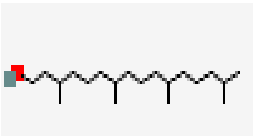
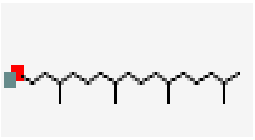
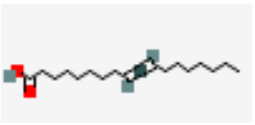
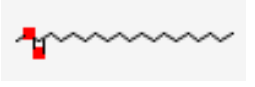
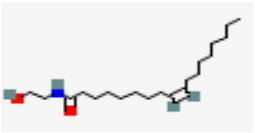
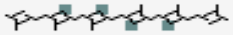
23.	1,2,3,4-tetrahydroiso-quinolin-6-ol-1-carboxylic acid	33.908	7.59		It is an antimicrobial and therapeutic agents	[82]
24.	2-(ethylenedioxy) ethylamine, N-methyl-N-[4.(1-pyrrolidinyl)-2-butynyl]-	34.866	1.67		It was reported for its antioxidant, anti-inflammatory, anticancer, antihypertensive potential.	[83]
25.	Ethanol, 2-(9-octadecenyloxy) -,(Z)-	37.404	2.54		It is reported as an anticancer agent	[84,85]
26.	1-heptatriacotanol	37.914	1.53		It is a growth stimulant for many plants and it increases the number of basal breaks.	[86,87]
27.	Oxiraneundeca noic acid, 3-pentyl-, methyl ester, trans-	38.378	2.06		It has medicinal value in antioxidant and anticancer agent	[88–91]
28.	Estra-1,3,5(10)-trien-17b-o1	38.826	8.14		It has been associated with treatment of as breast cancer, ovarian tumors, endometriosis.	[92]
29.	Phytol	39.737	12.12		It is used as an anticancer, hypoglycemic, antimicrobial and anti-inflamatory agent.	[93–95]

Table 3: Phytochemicals of methanolic extract of *F. exasperate* leaves

S/N	Chemical compound	RT (mins)	Area %	Chemical structure	Medicinal use	Reference
1	Dodecanioc acid, methyl ester (Lauric acid)	29.132	7.92		Used for the treatment of acne	[96,97]
2	Methyltetradecanoate (Mysteric acid)	34.788	3.24		It has been reported as an antifungal agent.	[98]
3	3,7,11,15,-tetramethyl-2-hexadecen-1-o1	37.396	3.24		Used for antibacterial, antimicrobial and anti-inflammatory activities.	[49,99]
4	3,7,11,15,-tetramethyl-2-hexadecen-1-o1	37.906	1.84		It is use for antimicrobial and anti-inflammatory	[49,99]
5	Hexadecanioc acid, methyl ester (palmitic acid)	38.378	10.88		It is used for various kind of esternal medicament; such as anodyne, itch-killer, disinfecting agents and skin softening.	[100,101]
6	9,12,-octadecadienoic acid (z,z)-, methyl ester	39.611	8.42		It can reduce the coronary heart disease and it can also help in preventing arthritis.	[102,103]
7	9-octadecenioc acid acid (z)- methyl ester	39.611	8.42		It has health-modulatory effects (anti-inflammatory, cardio-protective)	[104]
8	Phytol	39.745	28.83		It is an anticancer, antimicrobial agent.	[105,106]
9	Methyl stearate	39.807	3.97		It acts as an antileukemia	[107]
10	9-octadecenioc acid, 12-hydroxy-, ester, [(R-(Z)]	40.687	2.81		It is an anti-inflammatory	[108,109]
11	18,19-secoyohhimban-19-	42.133	1.04		It has been reported to improve	[110]

	oic acid, 16,17,20,21-tetradehydro-16-(hydroxymethyl)-, methyl ester (15B,16E)				and increase epididymal spermatocytes reserve in adult male	
12	squalene	44.788	11.47		It prevents cancer and also an antioxidant, it is also an antitumor	[111,112]

Antidiabetic activity of aqueous-methanolic extracts of *F. exasperate* leaves

Figure 1 illustrates the α-amylase inhibitory activity of the methanolic and aqueous extracts of *Ficus exasperata*. The results indicate that α-amylase inhibition increased in a concentration-dependent manner for both extracts. The aqueous extract exhibited a statistically significant inhibitory effect ($p = 0.049$), with an inhibition coefficient of 0.208 mL/µg, representing approximately 32.82% greater inhibitory efficiency compared to the methanolic extract (0.1566 mL/µg).

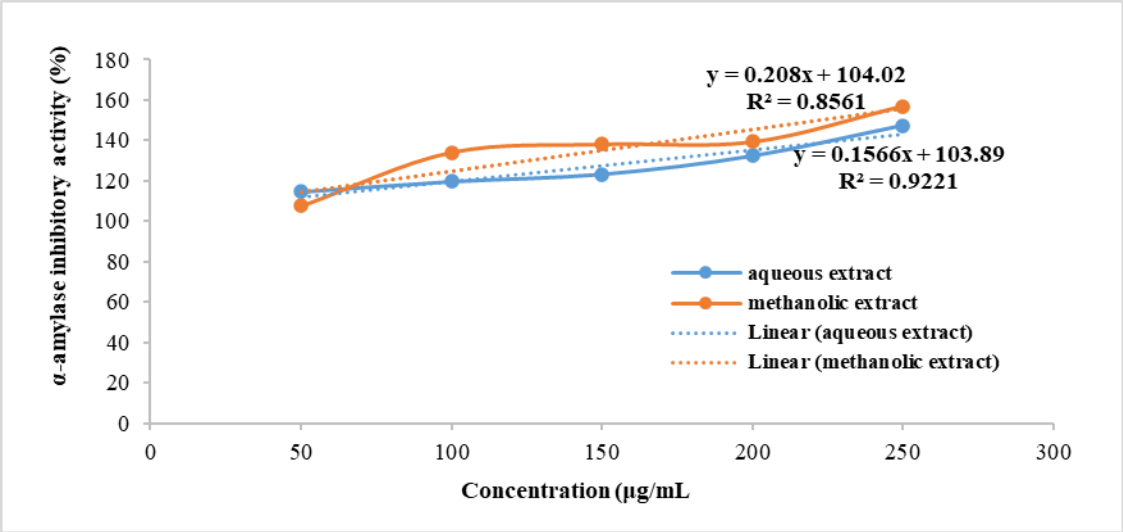


Figure 1: Alpha amylase inhibitory activity of *F. exasperata* leaves extract

Figure 2 illustrates the α-glucosidase inhibitory activity of the methanolic and aqueous extracts of *Ficus exasperata* leaves. The inhibition exhibited a concentration-dependent pattern for both extracts, with high coefficients of determination ($R^2 = 0.910$ and 0.892 for aqueous and methanolic extracts, respectively), indicating a strong fit of the regression model. Compared with the standard drug acarbose (IC_{50} = 16.5 µg/mL), both extracts demonstrated moderate inhibitory activity, with IC_{50} values of 47.78 µg/mL (aqueous) and 47.68 µg/mL (methanolic), as presented in Table 2. There was no statistically significant difference between the inhibitory activities of the aqueous and methanolic extracts ($p = 0.052$). However, the methanolic extract exhibited a slightly higher inhibitory efficiency ($1/IC_{50}$ = 0.168 mL/µg) compared to the aqueous extract (0.1842 mL/µg), although this difference was not statistically significant.

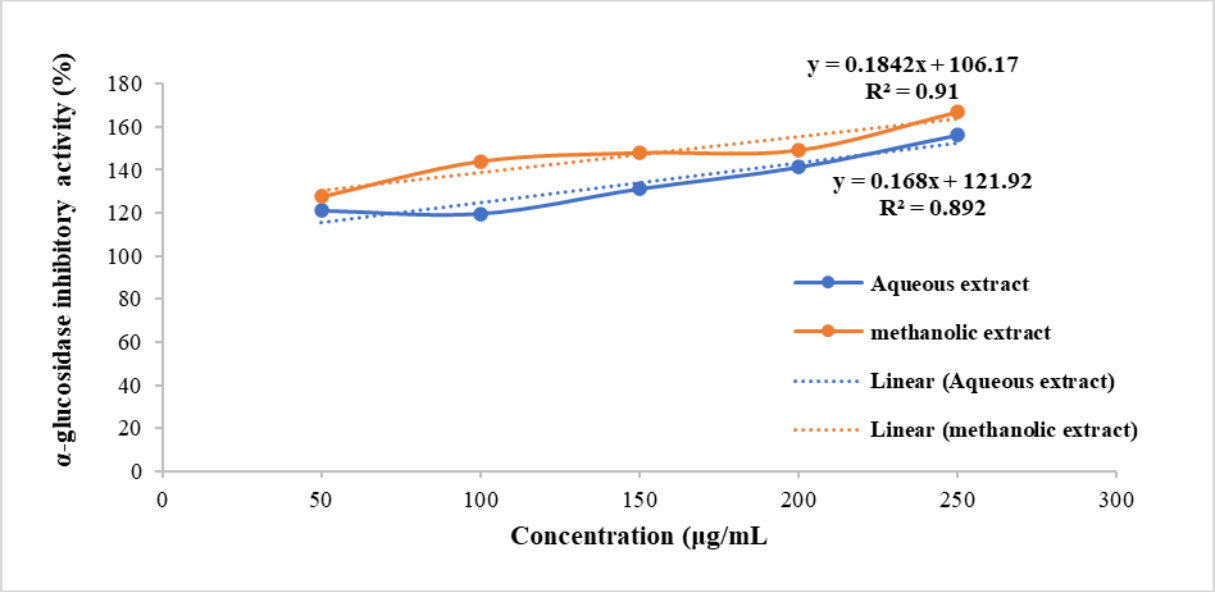


Figure 2: Alpha glucosidase inhibitory activity of *F. exasperata* leaves extract

Table 4: IC_{50} values of extracts and acarbose for α-amylase and α-glucosidase activities

Inhibitors	IC_{50} (µg /mL)	
	α-amylase	α-glucosidase
Aqueous extract of *F. exasperate* leaves	41.186	47.681
Methanolic extract of *F. exasperate* leaves	61.427	47.78
Acarbose	0.027	16.8

Antioxidant activity of extracts of *F. exasperata* leaves

Figure 3 represents the DPPH free radical scavenging activity of the aqueous and methanolic extracts of *Ficus exasperata* leaves. Both extracts exhibited a concentration-dependent increase in scavenging activity across the tested range (10–50 µg/mL). At 10 µg/mL, the aqueous extract demonstrated a higher scavenging activity (approximately 100%) compared to the methanolic extract (approximately 88%). Statistical analysis revealed a significant difference ($p < 0.0001$) between the DPPH scavenging activities of the aqueous and methanolic extracts at all tested concentrations. The coefficient of determination (R^2) for the aqueous extract was 0.87, indicating a strong linear relationship between concentration and scavenging activity, while the methanolic extract showed a moderate relationship with an R^2 value of 0.70.

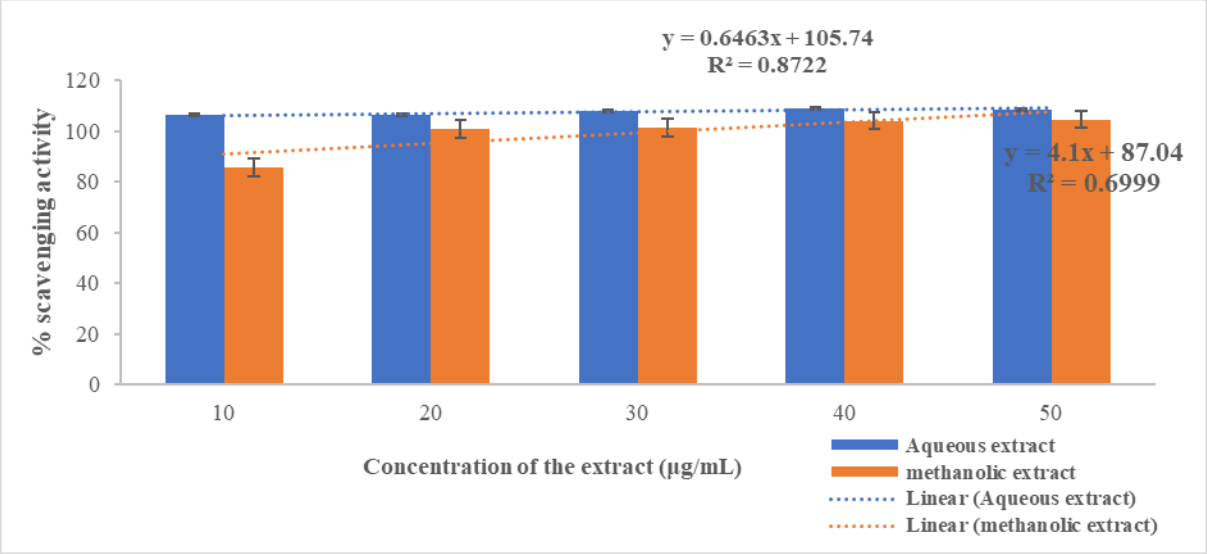


Figure 3: DPPH scavenging activity of extracts of *F. exasperata* leaves

Figure 4 presents the ABTS radical scavenging activity of both methanolic and aqueous extracts of *F. exasperata* across varying concentrations. The results show that antioxidant activity increased with concentration for both extracts. At lower concentrations (10 µg/mL and 20 µg/mL), the methanolic extract exhibited higher inhibitory activity (98–100%) compared to the aqueous extract (85–88%). However, at higher concentrations (20–50 µg/mL), both extracts demonstrated enhanced activity, with the aqueous extract showing a significantly higher $ABTS^{+}$ inhibitory effect overall ($P = 0.003$).

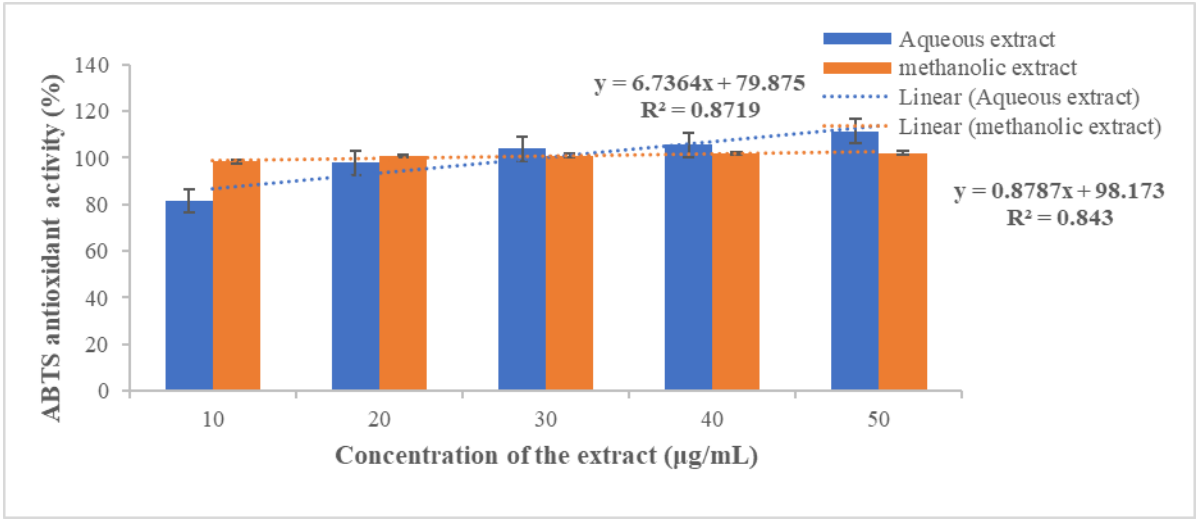


Figure 4: ABTS antioxidant activity of extracts of *F. exasperata* leaves

Table 5 shows the FRAP, H_2O_2 and SOD ion scavenging activities of methanolic and aqueous extracts of F. exasperate leaves. Result shows that both extracts exhibited lower ferric reducing antioxidant power (FRAP) compared to the control (0.1145 µg/100 g). However, the aqueous extract showed relatively higher reducing capacity than the methanolic extract. For hydrogen peroxide (H_2O_2) scavenging activity, the methanolic extract demonstrated higher activity (0.151613 µg/100 g) than the aqueous extract (0.090323 µg/100 g), although both were lower than the control value (0.2984 µg/100 g). Similarly, in the superoxide dismutase (SOD)-like activity assay, the methanolic

extract (0.029 µg/100 g) exhibited slightly higher activity than the aqueous extract (0.021 µg/100 g), but both remained below the control (0.073 µg/100 g).

Table 5: FRAP, H_2O_2 and SOD ion scavenging activities of *F. exasperate* leaves

Sample	FRAP (µg/100g)	H_2O_2 scavenging activity (µg/100g)	SOD ion scavenging activity (µg/100g)
Aqueous extract	0.026481	0.090323	0.021
Methanolic extract	0.01972	0.151613	0.029
Control	0.1145	0.2984	0.073

DISCUSSION

Plants, algae, and some essential oils contain phytol, which is an acyclic diterpene alcohol produced by the hydrolysis of chlorophyll [113]. Its anticancer, antioxidant, antibacterial, and anti-inflammatory properties are well known [114–116]. According to reports, phytol modulates oxidative stress and mitochondrial pathways to cause cancer cells to undergo apoptosis [117]. Its capacity to scavenge free radicals and prevent lipid peroxidation is responsible for its antioxidant action, which shields cellular components from oxidative damage [115]. Using in silico docking with important glucose-metabolizing enzymes and in vivo diabetic rat tests, Elmazar *et al*., [118] evaluated the antidiabetic effect of phytol and discovered that it greatly decreased fasting glucose and enhanced insulin sensitivity. Pro-inflammatory mediators such TNF-α, IL-6, and nitric oxide synthase pathways are modulated by phytol as part of its anti-inflammatory effect [95]. One important phenolic component, phenol, 2-methoxy-, has been shown to have antioxidant [64,65], antibacterial [119], cardioprotective [120] and anti-inflammatory properties [120,121]. Squalene is a natural triterpene and precursor of sterol biosynthesis, possesses significant antioxidant, anticancer, hepatoprotective, hypolipidemic, and immunomodulatory properties [122,123]. Its antioxidant activity is due to its ability to quench singlet oxygen and stabilize cellular membranes against oxidative degradation [123].

The presence of bioactive components like hexadecanoic acid, R-limonene, phytol, 9,12-Octadecadienoic acid (Z,Z) methyl ester, estra-1,3,5(10)-trien-17β-ol, 9-Octadecenoic acid (Z) methyl ester, and dodecanoic acid in this study validated the traditional use of *F. exasperata* leaf extracts for the treatment of Type 2 diabetes. Estra-1,3,5(10)-trien-17β-ol scaffold (and derivatives thereof) has been used to develop steroidal enzyme inhibitors such as 17β-HSD1 and steroid sulfatase, which are relevant to estrogen-dependent tumors such as breast cancer [92,124]. 1,2,3,4-tetrahydroisoquinolin-6-ol-1-carboxylic acid has been reported to exhibited antimicrobial and neuroprotective potential [125], while 2-methyl-4-vinylphenol contributes to antioxidant and flavor-enhancing effects, indicating its potential use in nutraceutical formulations [76]. The presence of Dodecanoic acid, Squalene, 9,12-Octadecadienoic acid (Z,Z) methyl ester, 9-Octadecenoic acid (Z) methyl ester, Hexadecanoic acid, *R-limonene* and *phytol* accounts for the use *Ficus exasperate* plant extract as a hypoglycemic and antioxidant agent.

Widyawati *et al*., [126] assessed the antidiabetic and antioxidant properties of squalene and found that squalene inhibited α-amylase and α-glucosidase enzymes, lowered fasting glucose, and enhanced antioxidant enzyme activity. Younis *et al*. [127] reported methyl oleate as a key active component contributing to glucose-lowering and antioxidant effects via α-glucosidase inhibition and oxidative stress reduction. *d-Limonene*, a monocyclic monoterpene, significantly reduced blood glucose and lipid peroxidation levels while enhancing antioxidant enzyme activity in streptozotocin-induced diabetic rats, demonstrating potent antihyperglycemic efficacy [128,129]. The combination of these active compounds supports the use of Ficus exasperate as a pharmacological agent in treating infections [130], as antioxidative / anti-arthritic agent [47] , hypoglycemic agent [131], and inflammatory disorders [132].

Figure 1 shows that aqueous extract demonstrated a stronger effect on α-amylase inhibition per unit mass, possibly because of increased enzyme affinity or

synergistic interactions among its hydrophilic phytochemicals. This result is consistent with that of Kazeem *et al*., [15], who discovered that among *F. exasperata* extracts, aqueous extract was the most efficient inhibitor of α-amylase and α-glucosidase. Water-based preparations of *F. exasperata* are reported to be more successful in controlling Type 2 diabetes, according to [41]. This may be because hydrophilic bioactive components are more soluble and bioavailable in aqueous mediums. With coefficient of determination (R^2) values of 0.8561 and 0.9221 for the aqueous and methanolic extracts, respectively, the results fit non-linear regression models well (Figure 1). Compared to acarbose (0.027µg/mL), dose-response analysis showed IC_{50} values of 41.186 µg/mL for the aqueous extract and 61.427 µg/mL for the methanolic extract (Table 4). Despite having a far higher potency than both plant extracts, acarbose has been connected to gastrointestinal side effects as bloating, diarrhea, flatulence, and abdominal discomfort [15,133], making *Ficus exasperate* extracts a safer choice.

The observed concentration-dependent α-glucosidase inhibitory activity of both methanolic and aqueous extracts of *Ficus exasperata* indicates that the bioactive constituents within the extracts interact progressively with the enzyme as their concentration increases. The high coefficients of determination (R^2 = 0.910 for aqueous and 0.892 for methanolic extracts) as shown if Figure 2 further support the reliability of the dose–response relationship, suggesting that the inhibitory effects are systematic and not due to random variation. This is consistent with the findings of Xiao *et al*. [52], who found significant α-glucosidase inhibitory effects in leaf extracts from *F. exasperata.*

Antioxidant-based therapies are gaining popularity as a useful therapeutic strategy and oxidative stress has been associated with the emergence of numerous metabolic disorders, including diabetes, arthritis, cancer, aging, and liver diseases [134]. DPPH evaluates a substance's capacity to scavenge free radicals. Figure 3 showed a dose-dependent response of both extracts. The aqueous extract showed greater scavenging action (approximately 100%) at 10 µg/mL than the methanolic extract (approximately 88%). A higher R^2value (0.87) was obtained for aqueous extract indicating a stronger linear relationship between concentration and scavenging activity, whereas a moderate R^2-value (0.7) was obtained for methanolic extract. This suggest that water-soluble phytochemicals such as phenols, 3-tert-butyl-4-hydroxyanisole (BHA) and 2-methyl-4-vinylphenol (p-Vinylguaiacol), present in this study contribute strongly to the antioxidant power. This finding opposes that of Shodehinde & Oboh [135] who found the DPPH free radical scavenging ability of methanolic extract of *F. exasperate* leaves to be more than that of aqueous extract at any extract concentration. Plants naturally produce phenolic chemicals as part of their secondary metabolism, as molecular structure enables them to donate electrons, bind to metal ions, and block enzymes like lipoxygenase, and neutralize free radicals. Phenolics function as potent and efficient antioxidants because they readily give up hydrogen atoms [136].

The capacity of antioxidant compounds to quench the long-lived ABTS+ radical is assessed using the ABTS technique [137]. The higher antioxidant activity of the methanolic extract at lower concentrations observed in Fig. 4 suggests a stronger initial capacity to quench $ABTS^+$ radicals. However, the superior performance of the aqueous extract at higher concentrations may be attributed to its enrichment in polar phenolic compounds and hydroxylated aromatic constituents identified in *F. exasperata*. These include phenol, 2-methoxyphenol, 2-methyl-4-vinylphenol, formic acid 2,6-dimethoxyphenyl ester, and other dimethoxyphenyl esters. Such compounds are known to possess electron-donating hydroxyl and methoxy groups, which enhance their ability to transfer electrons or hydrogen atoms to neutralize $ABTS^+$ radical cations. This mechanism stabilizes the resulting phenoxyl radicals, thereby contributing to the observed higher scavenging capacity of the aqueous extract [138,139].

When compared to the control (0.1145µg/100g), both extracts showed noticeably lower reducing capacity, suggesting that the extracts' intrinsic antioxidant strength is still much lower than the reference standard. The presence of hydrophilic phenolic compounds, including phenol, 2-methoxyphenol, 2-methyl-4-vinylphenol, and 3-tert-butyl-4-hydroxyanisole, which all have hydroxylated aromatic structures with a high capacity to donate electrons, is responsible for the aqueous extract's superior FRAP activity [140,141]. Studies have shown that the antioxidant ability of medicinal plants is correlated with their phenolics [142]. According to Wang *et al*. [143], hydrophilic extracts from medicinal plants had higher FRAP activity than their lipophilic counterparts due to the effective extraction of polyhydroxylated

chemicals, which easily donate electrons to neutralize reactive oxygen species (ROS).

According to Hiller *et al*. [144], hydrogen peroxide ($H2O_2$) is a non-radical but membrane-permeable ROS that produces hydroxyl radicals through the Fenton reaction, which oxidizes DNA, proteins, and lipids. Protein denaturation, DNA strand breakage, and lipid peroxidation can all be caused by these radicals. Table 4 shows that methanolic extract had a greater $H2O_2$ scavenging activity (0.151613 µg/100 g) than aqueous extract (0.090323µg/100 g), while both results were less than the control (0.2984 µg/100 g). The presence of non-phenolic phytochemicals like terpenoids, squalene, and phytol in this study, may be attributed for the strong electron- or hydrogen-donating capacity of methanolic extract of *F. exasperata* leaves, despite the absence of phenolics [115,122]. Gülçin [65] showed that the presence of hydroxylated aromatic compounds is directly linked to the ability of a plant extract to scavenge hydrogen peroxide. The main reactive oxygen species produced during aerobic metabolism are superoxide radicals (O_2^-), which combine with nitric oxide to produce the extremely reactive oxidant peroxynitrite. By catalyzing the dismutation of O_2^- into H_2O_2 and O_2, superoxide dismutase (SOD) provides the initial enzymatic defense [145]. The SOD-like scavenging activity of the methanolic extract was slightly greater (0.029 µg/100g) than that of the aqueous extract (0.021 µg/100g), although it was still lower than that of the control (0.073 µg/100g). The presence of bioactive substances like phytol and squalene, which have been demonstrated to modify endogenous antioxidant enzymes and improve superoxide neutralization, may be connected to the activity seen in the methanolic extract [146].

CONCLUSION

This study shows the strong antioxidant and antidiabetic potential of the aqueous and methanolic extract of *Ficus exasperata* leaf, with key bioactive components such as phytol, Phenol, 2-methoxy-, responsible for these effects. Both aqueous and methanolic extracts inhibited α-amylase and α-glucosidase, with the aqueous extract showing superior α-amylase inhibition and the methanolic extract exhibiting greater α-glucosidase suppression.

Antioxidant assays revealed that the aqueous extract was superior in DPPH, ABTS and FRAP assays, whereas the methanolic extract exhibited higher H_2O_2 and SOD-like activities. These activities are attributable to the differential extraction of phenolics and other bioactive constituents. The results validate the traditional use of *F. exasperata* leaves for medicinal health, functional food and nutraceuticals applications, due to their antioxidant properties.

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AUTHOR'S CONTRIBUTION

DSO conceived and designed the study, performed the experimental work, analyzed the data, and drafted the manuscript. TOA contributed to the study design, supervised the research, and critically revised the manuscript. CCO assisted in data collection, laboratory analysis, and manuscript editing. ICE contributed to data interpretation and proofreading of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that no personal or financial conflicts of interest influenced the conduct or outcomes of this research. All contributors confirm that they maintained complete independence, with no commercial or financial relationships that could be perceived as potential sources of bias during the study.

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