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PHYTOCHEMICAL, CYTOTOXIC AND ALPHA-AMYLASE INHIBITORY ACTIVITIES OF TWO MEDICINAL PLANTS USED IN THE MANAGEMENT OF *Diabetes Mellitus:* A COMPARATIVE STUDY

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ABSTRACT

Hunteria umbellata (K. Schum.) Hallier f. and *Acacia nilotica* (L.) are two common medicinal plants traditionally used to manage *Diabetes mellitus* and other degenerative diseases. This study aims to investigate the cytotoxic and alpha-amylase inhibitory activities of the crude ethanol seed extracts of *H. umbellata* (HUSE) and *Acacia nilotica* (ANSE). The dried and ground plant materials were extracted separately by macerating in ethanol for 72 h. The flavonoid extracts were obtained from the plant materials using the Harborne method. The cytotoxic activity was determined using the brine shrimp lethality assay (BSLA). The alpha-amylase inhibitory assays were carried out preliminarily using the starch-iodide assay. The component flavonoids of the crude flavonoid extract were determined using High-Performance Liquid Chromatography (HPLC). Both crude extracts, HUSE and ANSE, exhibited remarkable cytotoxic activity, with LC_{50} values of 52.05 ± 5.00 µg/mL and 75.56 ± 0.10 µg/mL, respectively. HPLC detected quercetin, ferulic, rutin, catechin, and apigenin in the two extracts. The most abundant flavonoid in both extracts is quercetin, 30.64% in HUSE and 26.87% in ANSE. Both extracts showed alpha-amylase inhibitory activities. The two plants may be explored for new cytotoxic and antidiabetic agents.

Keywords: Hu*nteria umbellata* seed, *Acacia nilotica* seed, Phytochemical, Cytotoxic activity, alpha-amylase inhibitory activity, flavonoid contents, High-Performance Liquid Chromatography.

INTRODUCTION

Human beings have always depended on nature to produce shelter, food, clothing, fertiliser, means of transportation, flavours, and medicine [1]. Plants have been used in herbal medicine practices in many countries, based on traditional knowledge passed down from one local community to another through several generations, either orally or in written form [2]. The passing of knowledge has been enhanced in recent times through the study of ethnopharmacology [2]. Although a large number of conventional drugs are based on herbal medicines, the main difference between the two is that the latter contains a large number of chemicals (consisting of both primary and secondary metabolites) rather than a single pharmacologically active substance, which acts

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on one another to moderate or enhance an effect [3].

Africa has between 5000 and 6000 kinds of significant medicinal plants and flora [4, 5]. These plants have been used as an elixir in the treatment of numerous maladies due to their widespread availability, affordability, and supposed usefulness based on ancient customs and beliefs [6]. Additionally, several of these therapeutic plants boost the economies of several nations through exports and sales [7-9]. Based on their recorded folkloric usage and ethnobotanical surveys, these plants have also been the subject of diverse pharmacological research, evaluations, and validations [10]. Numerous of these plants have been shown in scientific studies to elicit a wide range of biological functions based on empirical data. Additionally, the possible mechanisms of action and active principles for the detected pharmacological activities have been clarified [6]. Many therapeutic plants contain significant amounts of secondary metabolites, including alkaloids, flavonoids, terpenoids, and saponins, among others [11, 12]. Some of these metabolites have been used or developed into drugs for the treatment of infectious disorders, malaria, metabolic syndrome and other diseases [13, 14]. In many developing nations, people still rely on herbal preparations as a panacea for various ailments [15, 16]. For example, in China and some Asian countries, such herbal preparations account for about 30–50% of medicinal consumption [15, 16].

Flavonoids are polyphenolic secondary metabolites found in flower pigments, vegetables, fruits, and beverages such as wine, tea, and cocoa [17]. Flavonoids have been reported to be favourable antioxidants in managing diseases such as cancer, Alzheimer's disease, and atherosclerosis. Flavonoids also have protective functions in the Human body systems due to their unique activities as antioxidants, anti-inflammatory agents, anti-mutagenic agents, and anti-carcinogenic agents. The unique medicinal properties of flavonoids make them valuable in the pharmaceutical and cosmetic industries [17].

Hunteria umbellata and *Acacia nilotica* are two common plants in the western part of Nigeria that have featured in ethnobotanical studies as useful plants used in the management and treatment of cancer and *D. mellitus* in traditional practices [18-22]. *Hunteria umbellata* belongs to the Apocynaceae plant family, which comprises 4,555 species of trees, shrubs, woody vines, and herbs [23]. It is commonly found in West and Central African countries, including Cameroon, Senegal, Ghana, Gabon, the Democratic Republic of the Congo, Liberia, Guinea-Bissau, Sierra Leone, the Ivory Coast, and Nigeria [24]. The plant is known by different local names depending on the tribe; for example, it is known

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as "Osu", "Npokiri", and "Abeere" or "Erin" among the Edo, Igbo, and Yoruba people of Nigeria, respectively [25]. *Acacia nilotica* belongs to the family Fabaceae and sub-family Mimosoideae. It is a well-distributed tropical tree plant known as Booni in the Yoruba-speaking part of Nigeria [26].

Hunteria umbellata has been documented to possess numerous local and folkloric medicinal properties [27-29]. The seed and bark are prepared as infusions and decoctions and are effective against fever, leprosy sores, menstrual disturbances, infertility, intestinal worms, abdominal colic, discomfort, and stomachache [27]. This plant possesses an antipyretic property, which is comparable to that of aspirin [28, 29]. According to some studies, *H. umbellata* is useful to men as a sexual health booster, especially for its erection-stimulating abilities and the aphrodisiac properties of the fruit [30, 31]. The use of *H. umbellata* seed in the local management of *Diabetes mellitus* has been confirmed in an *in vivo* study in rats [32-33]. Erinidine, a potent anti-diabetic drug, was isolated from *H. umbellata* [34].

Acacia nilotica (L), also known as *Vachellia nilotica*, has been featured in numerous research studies as a multipurpose plant. Its various plant parts are reported to be beneficial for the treatment of diseases such as cancer, *Diabetes mellitus, cough, asthma, Tuberculosis,* sore throat*, bronchitis, urinary tract infections, diarrhoea, toothache, and* bronchitis [26, 35, 36]. It is also used traditionally to treat cancers and tumours [26, 37]. The antidiabetic activities of the various parts were reported [38, 39].

This work aims to evaluate the phytochemical contents, cytotoxic and alpha-amylase inhibitory activities of *H. umbellata* seed and *A. nilotica* seed ethanol extracts. The phenolic contents of the two plant extracts were determined and compared using HPLC. The cytotoxic and alpha-amylase inhibitory activities of the crude extracts and flavonoids were also determined and compared.

MATERIALS AND METHODS

Chemicals and reagents

All solvents used: Methanol, ammonium hydroxide, hydrochloric acid, Dimethyl sulfoxide (DMSO), and other chemicals were of analytical grade and were purchased either from Sigma-Aldrich Chemical Company or Fisher Scientific Chemical Company. HPLC-grade acetonitrile and formic acid (Sigma-Aldrich Chemical Company) were used for the HPLC work. *Artemia salina* (Aqua master, China) was used for the cytotoxicity assay. The pancreatic alpha-amylase (EC 3.2.1.1; Sigma-Aldrich Chemical Company) and potato starch (from North Carolina) were used in the starch-iodide assay.

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HPLC data were obtained using an Agilent HPLC1260 (Agilent Technologies, Germany).

Collection and preparation of plant material

The plant materials, *Hunteria umbellata* seeds *and Acacia nilotica* seeds, were bought from the Mushin market and authenticated at the University of Lagos herbarium, with voucher numbers LUH 100583 and LUH 100584, respectively. The plants were air-dried for several weeks and then ground using an electric blender. The ground plant materials were stored in plastic containers until needed for analysis.

Extraction of plant materials

Hunteria umbellata ethanol seed extract

The ground *H. umbellata* plant seed (283.23 g) was extracted by macerating in 80% ethanol (1000 mL) for 72 h. The extract was filtered to obtain the ethanol extract (HUSE), which was then concentrated to dryness using a rotary evaporator and an air drier and stored at 4 °C until required for further work.

Acacia nilotica ethanol seed extract

The ground *Acacia nilotica* whole seed (300 g) was extracted by macerating in 80% ethanol (1000 mL) for 72 h. The extract was filtered out to obtain the ethanol extract (ANSE). The extract was concentrated to dryness using a rotary evaporator and an air drier and then kept at 4 °C until required for further work.

Qualitative phytochemical screening

The plant extracts were screened for secondary metabolites using standard methods previously described [40].

Extraction and determination of flavonoids

Flavonoids were extracted from the two plant materials using Harborne's method [41]. Aqueous methanol (80%, 50 cm^3) was added to 10 g of the coarse plant sample in a 250 cm^3 beaker, covered, and allowed to stand for 24 h at room temperature. The extract was separated from the residue using Whatman filter paper number 42 (125 mm). The residue was further re-extracted with the same volume of methanol (three times). The extract was pooled together and then transferred into a crucible, where it was evaporated to dryness over a water bath. The crucible content was cooled in an oven at 40°C and weighed until a constant weight was obtained. The experiment was conducted three times, and the percentage of crude flavonoid obtained was calculated.

High-Performance Liquid Chromatography (HPLC)

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The component compounds in the crude flavonoid were determined using HPLC. The extract (10 mg) was dissolved in HPLC grade methanol 5 mL, the samples were filtered and the filtrate was cleaned up before injection for analysis 10 µg of the samples was injected into the mobile phase and then run on the HPLC Machine (Agilent 1260; column: zorbax eclipses, dimension:150×4.6; mm, flow rate;7 mL\min). The mobile phase is a mixture of acetonitrile and 0.1% formic acid, run in gradient elution mode [42].

Cytotoxicity Assay

Cytotoxic activity was investigated using the brine shrimp lethality test as previously described [42]. *Artemia salina* Leach (brine shrimp egg) was used as the test organism. Seawater was taken into the small tank, and shrimp eggs were added to one side of the tank. This side was covered. The eggs were left for 24 h under constant light and oxygen supply to hatch and mature into nauplii. The hatched shrimps are attracted to the light, so nauplii free from the shell are concentrated at the illuminated part of the tank, from where they are collected for the experiment. The nauplii (10) were taken using a micropipette into the sample bottles containing the solutions. To prepare the extract, each plant extract (32 mg) was dissolved in 0.2 mL of pure dimethyl sulfoxide (DMSO), and the volume was brought to 20 mL with seawater. The concentration of the stock solution was 1600 µg/mL, and the solution was serially diluted to 800, 400, 200, 100, 50, and 25 µg/mL with seawater. The experiment was carried out in triplicate.

Alpha-amylase Assay

The alpha-amylase inhibitory activities of plant extracts were determined using the starch iodide assay [43]. The plant extract (250 µL) in DMSO (concentration range: 0, 10, 100 µg/mL) was added to 250 µL of enzyme solution (250 µg/mL pancreatic alpha-amylase enzyme) dissolved in 0.02 M Sodium phosphate buffer with 0.006 M sodium chloride. The solution was incubated for 10 min at 37 °C. Soluble starch (potato starch, 1%, 250 µL) was then added to all the test tubes and incubated for 10 min at 37 °C. This was followed by the addition of 250 µL 1M HCl to terminate the enzymatic reaction, and then the addition of 100 µL of iodine reagent. The colour changes were observed and recorded.

Statistical Analysis

All analysis was carried out using Microsoft Excel. Results are presented as mean ± SD. All graphs were drawn using Microsoft Excel 2016. Means are compared using Student's t-test.

RESULTS AND DISCUSSION

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Extraction of plant materials

The plant extracts HUSE and ANSE, and the crude flavonoid extracts HUF and ANF were obtained. The percentage yields of each extract are summarised in Table 1.

Table 1: Crude *H. umbellata* and *A. nilotica* seed extracts and percentage yields

Plant Extract	Colour	Percentage yield	Plant Extract	Colour	Percentage yield
HUSE	Brown sticky solid	3.37 %	ANSE	Black solid	33.6%
HUF	Brown solid	0.37±0.01*	ANF	Black solid	1.32±1.02*

*: Mean of three experiments; HUSE- *H. umbellata* seed ethanol extract; HUF- *H. umbellata* seed flavonoid extract; ANSE- *A. nilotica* seed ethanol extract; ANF- *A. nilotica* seed flavonoid extract.

Phytochemical screening

Phytochemical screening of the plant extracts reveals variations in their phytochemical contents. Alkaloids, saponins, steroids, flavonoids, phenols, cardiac glycosides and anthraquinones are found in both plant extracts. Tannins are not detected in the *A. nilotica* seed extract (ANSE).

Medicinal plants contain secondary metabolites such as alkaloids, flavonoids, terpenoids, and saponins, among others, which are responsible for their therapeutic purposes [11, 12]. These phytochemical contents explain the medicinal uses of these plants in various traditional practices and their roles in disease prevention and treatment [12].

Table 2. Phytochemical screening of crude *Hunteria umbellata* and *Acacia nilotica* ethanol seed extracts

Phytochemicals	HUSE	ANSE
Alkaloids	+	+
Saponin	+	+
Tannins	+	-
Steroids	+	+
Flavonoids	+	+

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Phenols	+	+
Cardiac glycosides	+	+
Anthraquinones	+	+

HUE-*Hunteria umbellata* seed ethanol extract; ANSE –*Acacia nilotica* seed ethanol extract

Flavonoid Contents of Extracts from HPLC

The HPLC was used to determine the polyphenolic contents of the plant materials. Gallic acid, catechin, p-coumaric acid, ferulic acid, rutin, quercetin and kaempferol contents were determined by HPLC (Figures 1-3). The results suggested *p*-coumaric acid and kaempferol are found in *H. umbellata* but not in *A. nilotica*. Catechins are more abundant in the *A. nilotica* seeds than in *H. umbellata*; Gallic acid is absent in both extracts (Figure 3).

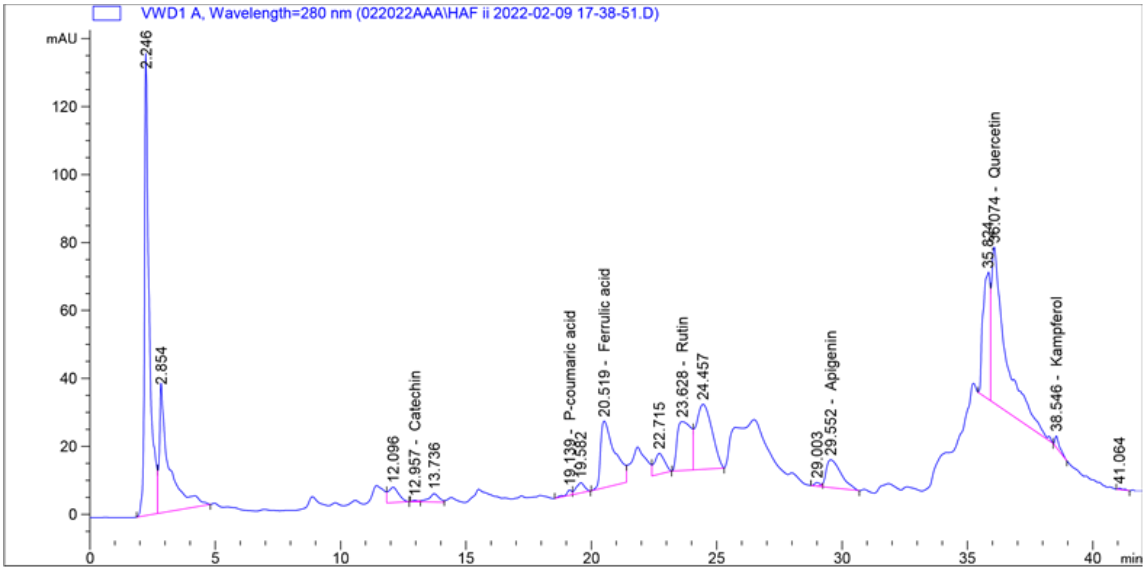

Figure 1. HPLC Chromatogram of *H. umbellata* crude seed extract

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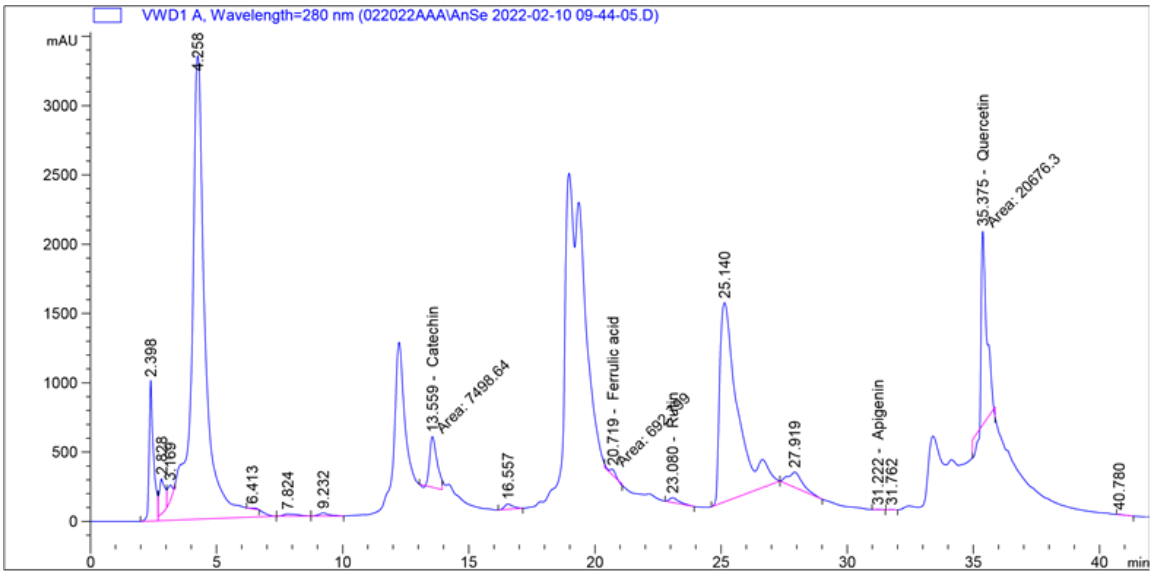

Figure 2: HPLC Chromatogram of *A. nilotica* seed extract

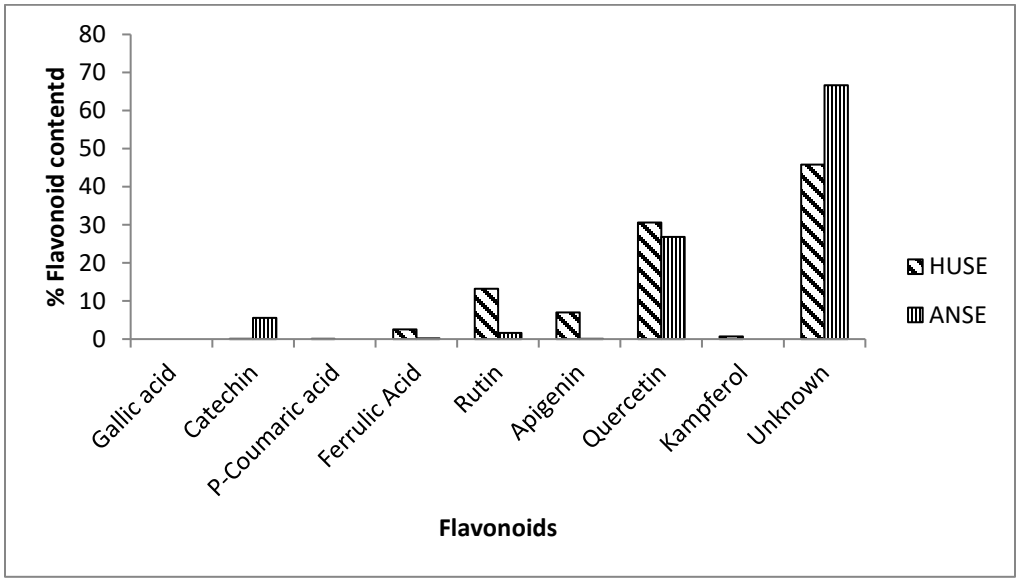

Figure 3. Comparative flavonoid contents of *H. umbellata* (HUSE) and *A. nilotica* (ANSE) extracts

The results indicated that the HUSE extract contains a higher percentage of major flavonoids, such as ferulic (2.54%), rutin (13.19%), and apigenin (6.98%), compared to the ANSE extract. The most abundant flavonoid in both extracts is quercetin (30.64% and 26.87%). The major flavonoids are indicated in Figure 4.

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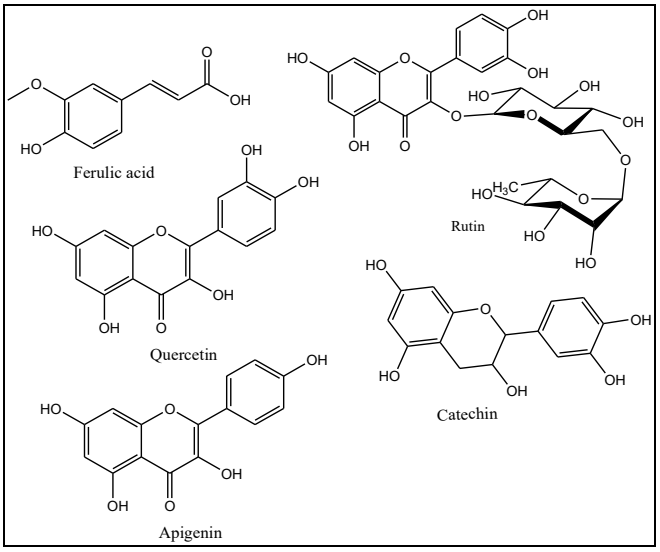

Figure 4. Major flavonoids common to *H. umbellata* and *A. nilotica* ethanol seed extracts

Flavonoids are a group of compounds that have been identified to possess diverse medicinal properties, including antioxidant, anticancer, anti-inflammatory, and anti-ageing effects [44-46]. Ferulic acid, catechin, *p*-coumaric acid, and apigenin are examples of such flavonoids that have been identified for their anti-ageing, anticancer, anticholesterol, and antioxidant properties [44-47]. Kaempferol and quercetin exhibit unique anticancer, anti-inflammatory, and antioxidant properties. [46, 48-50].

Cytotoxic Activity

The results of the cytotoxicity assay (Figures 5 and 6) indicated that the *H. umbellata* seed extract (HUSE) had an LC_{50} of 52.05±5.00 µg/mL, compared with the *A. nilotica* seed extract (ANSE), which had an LC_{50} of 75.56±0.10 µg/mL, suggesting that the two plant extracts are cytotoxic, with the most activity observed in HUSE. Typically, a low $LC_{50,}$ less than 1000 µg/mL is considered to suggest cytotoxic or anticancer activities [51, 52]. It has also been reported that plant extracts exhibiting anticancer properties in preliminary studies using BSLA with low LC_{50} values have been identified as sources of active compounds with anticancer properties [51, 53, 54]. Hence, it may be concluded that the *H. umbellata* seed and *A. nilotica* seed extracts have potential anticancer properties.

Quercetin, the most abundant flavonoid in both plant extracts, has been featured in several reports for its anticancer, antioxidant, and anti-inflammatory activities [48, 49]. Several types of

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cancerous situations, such as cervical, breast, prostate, lungs, and colon, have been reported to benefit from the peculiar anticancer properties of quercetin [48-50].

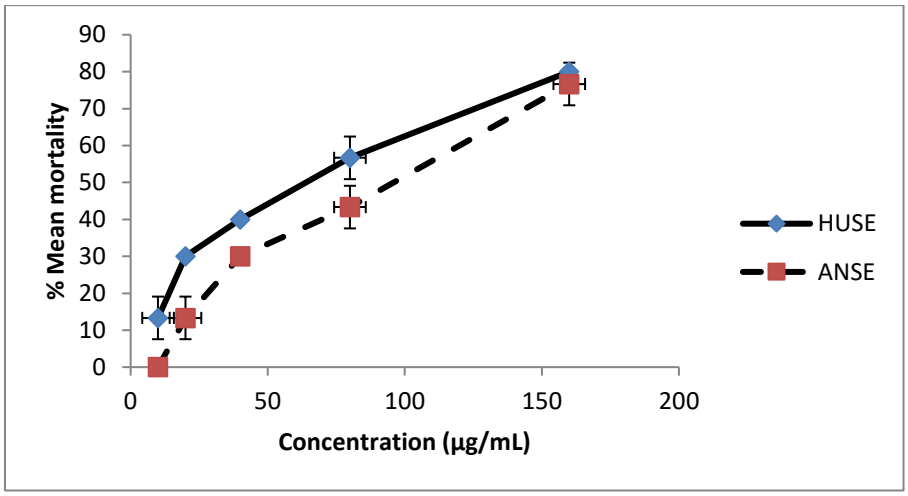

Figure 5. Mean percentage mortality of *H. umbellata* (HUSE) and *A. nilotica* (ANSE) at different concentrations

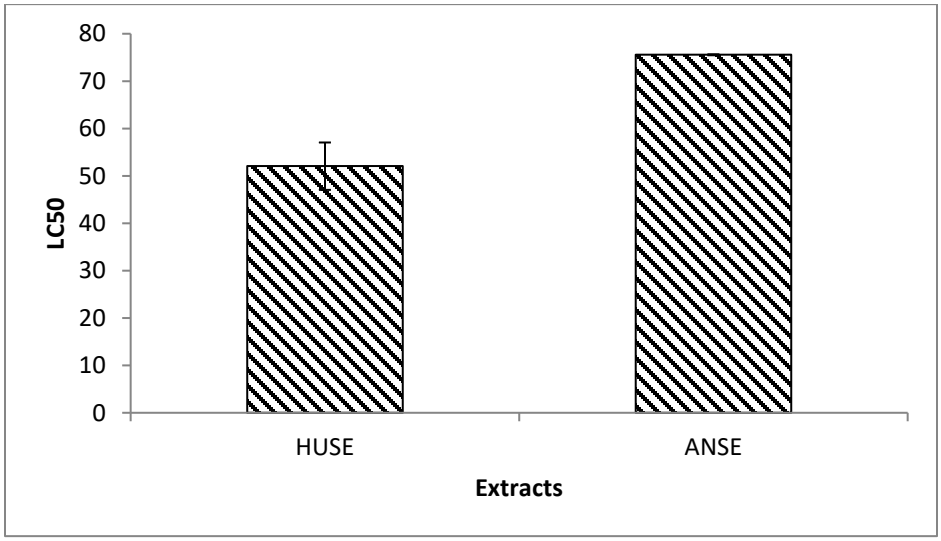

Figure 6. LC_{50} values for *H. umbellata* (HUSE) and *A. nilotica* (ANSE)

Alpha-amylase inhibitory activity

Table 4. Alpha-amylase inhibitory activity of crude *H. umbellata* (HUSE) and *A. nilotica* (ANSE) extracts

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Concentration (µg/ml)	HUSE	ANSE	Conclusion
0	Orange	Orange	No inhibition
1	Blue-black	Blue-black	Inhibition
10	Blue-black	Blue-black	Inhibition
100	Blue-black	Blue-black	Inhibition

The preliminary alpha-amylase inhibitory activities of the plant extracts, as determined by the starch-iodine assay, indicate a positive result for both plants studied. These results support the traditional uses of these plants for managing *D. mellitus,* further suggesting that the antidiabetic properties exhibited and explored in conventional practices may be due to the inhibition of digestive enzyme activities [26, 32-33]. The control of postprandial glucose concentration is one way to manage sugar levels in people with diabetes, thereby preventing nonenzymatic glycosylation of various proteins due to high sugar concentrations, which can lead to complications associated with *D. mellitus* [55]. Several literature reports have featured flavonoids as having the ability to inhibit the activities of digestive enzymes, such as alpha-amylase and alpha-glucosidase [56, 57]. Specific structural features of the flavonoid - a double bond between C2 and C3 and OH groups at A5 and B3- have been associated with their ability to inhibit alpha-amylase [57]. These features observed in the flavonoid structures of *H. umbellata* and *A. nilotica* further explain the alpha-amylase inhibitory activities observed in these two plants.

CONCLUSION

Hunteria umbellata seed and *Acacia nilotica* seed are known medicinal plants for their numerous folkloric and traditional benefits. The results of this study suggest that the two plants exhibit cytotoxic activity. The alpha-amylase inhibitory activity results also indicated that these plants can be used to manage *D. mellitus,* as explored by traditional practices. These plants contain relevant phenolic compounds to support the positive results for the biological activities exhibited in this work. These two common plants

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may be possible sources of anticancer and antidiabetic drugs.

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