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Phytochemical Composition, Antioxidant Activity, Cytotoxicity, And Antidiabetic Potential of Ethanol Extract of *Momordica charantia* Using Insulin-Resistant HepG2 Cell Lines

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ABSTRACT: The therapeutic potential of plant-derived bioactive compounds is increasingly recognized in the management of diabetes mellitus. This study investigated the phytochemical profile, antioxidant capacity, cytotoxicity, and antidiabetic activity of the ethanol extract of *Momordica charantia* using insulin-resistant HepG2 cell lines using appropriate standard methods. Qualitative and quantitative phytochemical analyses revealed the presence of multiple bioactive constituents, with tannins (92.97 ± 0.21 mg/100 g) as the most abundant, followed by saponins (56.87 ± 0.01 mg/100 g) and phenols (50.56 ± 0.01 mg/100 g), while anthraquinones were present at the lowest concentration (8.88 ± 0.73 mg/100 g). GC–MS profiling identified fifteen compounds, predominantly n-hexadecanoic acid (42.19%), neophytadiene (11.18%), and octadecanoic acid (9.75%). The extract exhibited appreciable antioxidant activity, as evidenced by ferric reducing power and effective scavenging of DPPH and nitric oxide radicals, with IC_{50} values of 78.40 µg/mL, 63.18 µg/mL, and 42.78 µg/mL, respectively. Cytotoxicity evaluation demonstrated a high IC_{50} value of 6183.52 µg/mL in HepG2 cells, indicating low cytotoxic potential. Additionally, the extract modulated insulin signaling by downregulating the expression of AKT, IRS, and PIP3 genes. Although these effects were less pronounced than those observed with metformin and did not fully restore normal gene expression, the results collectively suggest that *Momordica charantia* possesses significant antioxidant and antidiabetic properties, supporting its potential application as a complementary therapeutic agent in diabetes management.

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Diabetes mellitus remains a major global health burden, affecting 537 million individuals worldwide according to the International Diabetes Federation (IDF, 2021a), with rising prevalence particularly in

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low- and middle-income countries. Nigeria alone accounts for approximately 3.6 million adult cases (IDF, 2021b). The World Health Organization (WHO, 2022) reports that diabetes is a major cause of morbidity and mortality in Nigeria, especially among the urban population. The disease arises from impaired insulin production or utilization, leading to persistent hyperglycaemia and multiple organ complications. Diabetes mellitus is a major health issue in both developed and developing countries (Zhao *et al.*, 2021; Salamone *et al.*, 2021). There are different types of diabetes mellitus, but one of them is type 1 diabetes mellitus (T1DM). T1DM is mainly genetic and occurs when the pancreas is damaged and cannot make enough insulin (Bunyatyan *et al.*, 2017). Insulin resistance stands as a pivotal factor in the progression of type 2 diabetes mellitus (T2DM) and its associated complications (Bunyatyan *et al.*, 2017). Within the realm of diabetes mellitus, T2DM takes centre stage, impacting a remarkable 90% of the diabetes-afflicted population (Xu *et al.*, 2022). This prevailing prevalence accentuates the pressing need to revolutionize diabetes mellitus treatments, presenting a contemporary challenge of paramount medical and societal significance. Notably, the adept management of postprandial blood glucose levels emerges as a potential requirement in the landscape of diabetes care, holding promise to shape the course of this condition (Zhao *et al.*, 2018). While pharmaceutical therapies are available, many pose limitations including hypoglycaemia, gastrointestinal disturbances, and inadequate long-term efficacy (Lee *et al.,* 2014). Thus, there is a high demand for more potent and safer anti-diabetic agents from natural sources (Fauchier *et al.*, 2021; Preiato *et al.*, 2021). Consequently, natural products with antidiabetic properties have gained increased research attention. *Momordica charantia*, commonly referred to as bitter melon or bitter gourd, is a member of the Cucurbitaceae family and enjoys a broad geographical presence across tropical and subtropical areas, including Africa, South America Asia, the Caribbean and sections of the Amazon basin (Xu *et al.*, 2022). It is worth highlighting that the seeds and fruits of *Momordica charantia* boast a notable abundance of proteins, characterized by a quality that aligns with the amino acid criteria established by the World Health Organization for preschool children (Saeed *et al.*, 2018). Owing to its diverse array of health-enhancing attributes, including hypoglycemic, anti-cancer, antimicrobial, antioxidant, antifertility, antimutagenic, anthelminthic, and immunomodulatory capabilities, *Momordica charantia* has entrenched itself as a staple in traditional medicine. Its applications span an impressive spectrum, encompassing the treatment of ailments such as gout, leprosy, rheumatism, furuncles, jaundice, toothaches, piles, pneumonia, dysmenorrhea, psoriasis, diarrhoea, and eczema (Tan *et al.*, 2016; Jia *et al.*, 2017). Moreover, owing to its pronounced anti-diabetic attributes, *Momordica charantia* emerged as a potential powerhouse in the realm of dietary components and medical foods. This holds especially true for individuals grappling with diabetes or prediabetes, offering promise not only for blood sugar regulation but also for the management of body weight and lipid metabolism (Wang *et al.*, 2017).

Despite extensive ethnopharmacological use, cellular-level mechanistic data remain limited, particularly within hepatocellular insulin-resistant models such as HepG2 cells. This study therefore evaluates the phytochemical composition, antioxidant activity, cytotoxicity, and antidiabetic potential of the ethanol extract of *Momordica charantia* using insulin-resistant HepG2 cell lines

MATERIALS AND METHODS

Plant Collection and Authentication: The whole plant of *Momordica charantia* was collected from Isale Oba area, Igboora, Ibarapa Central Local Government Area of Oyo State, Nigeria, and authenticated by a botanist in the Department of Pure and Applied Botany, College of Biological Sciences, Federal University of Agriculture, Abeokuta. A voucher specimen was deposited with the herbarium under the reference number FHA-4289.

Extraction and Freeze Drying of Plant Material; Dried plant material was milled and extracted in 90% ethanol (1:10 w/v) for 72 hours. Filtrate was concentrated at 40 °C and freeze-dried at –55 °C under vacuum for 72 hours.

Qualitative Screening: Standard methods (Savithramma *et al.,* 2011; Pant *et al.,* 2017) were used to detect alkaloids, saponins, tannins, phenolics, steroids, flavonoids, terpenoids, cardiac glycosides, reducing sugars, and anthraquinones.

Quantitative Analysis; Levels of alkaloids, tannins, phenols, saponins, flavonoids, and terpenoids were quantified using established spectrophotometric protocols (Taiwo *et al.,* 2023; Bekoe *et al.,* 2020).

2, 2-Diphenyl-2-Picrylhydrazyl (DPPH) Scavenging Activity Assay: Antioxidant assay was performed using the method developed by Hassan *et al.* (2022). Briefly, 0.1 mM of DPPH solution in methanol: water (8:2, v/v) was prepared and then 1 mL of this solution with 1 mL of extract solution at concentrations range from 0 to 400 µg/mL was mixed. After 30 minutes,

the absorbance was measured at 517 nm. Decrease in the DPPH solution absorbance showed an increase in the DPPH radical scavenging activity. This activity is given as % DPPH radical scavenging which is calculated using the following equation 1:

$$\text{DPPH RS (\%)} = \frac{C_{AB} - S_{AB}}{C_{AB}} * 100 \quad (1)$$

Where DPPH RS = 2,2-diphenyl-1-picrylhydrazyl radical scavenging; C_{AB} control absorption; S_{AB} = sample absorption

Nitric Oxide Inhibition Assay: The assay methodology employed in this study closely followed the procedures outlined by Hassan *et al.* (2022) for evaluating the nitrite radical scavenging activity. To maintain consistency and accuracy, stock solutions of each extract fraction and ascorbic acid were prepared at a concentration of 100 mg/mL in methanol. These initial stock solutions were then subjected to serial dilution, yielding final concentrations of 25, 50, 75, and 100 µg/mL. In preparation for the assay, the Griess reagent, a crucial component, was meticulously concocted by thoroughly mixing equal proportions of two distinct components: 2% sulphanilamide in 5% phosphoric acid and 0.1% naphthyl ethylenediamine dihydrochloride. This reagent mixture was freshly prepared just before use to ensure its effectiveness. The core experimental procedure involved the combination of 50 µL of a 10 mM sodium nitroprusside solution (prepared at a concentration of 0.29 g/100 mL) with 50 µL of the various concentrations of extract fractions in individual wells of a 96-well plate. Subsequently, these combined solutions were allowed to incubate at a temperature of 25°C for a duration of 180 minutes. Following the incubation period, 100 µL of the previously prepared Griess reagent was meticulously introduced into each well containing the reaction mixture. To establish a control baseline, a sample devoid of extract fractions but containing an equal volume of methanol was concurrently prepared following the same procedures as the test samples. To quantify the extent of nitrite radical scavenging activity exhibited by the respective extract fractions and ascorbic acid, the absorbance of each sample was meticulously measured at a wavelength of 542 nm using a spectrophotometer. The percentage of nitrite radical scavenging activity for each fraction and ascorbic acid was then calculated utilizing the following formula 1:

Reducing Power Assay: the procedure involved preparing aliquots of varying concentrations of ascorbic acid (standard) and test samples (ranging from 25 to 100 µg/mL). These aliquots were dissolved in 1 mL of deionized water. Subsequently, the dissolved solutions were mixed with 2.5 mL of phosphate buffer (pH 6.6) and 2.5 mL of potassium ferricyanide (1%). The resulting mixture was incubated in a water bath at 50°C for 20 minutes, followed by cooling. To the cooled mixture, 2.5 mL aliquots of trichloroacetic acid (10%) were added. The combined solution was then subjected to centrifugation at 3000 rpm for 10 minutes. The upper layer of the solution (2.5 mL) was carefully separated and mixed with 2.5 mL of distilled water. To this solution, 0.5 mL of freshly prepared ferric chloride solution (0.1%) was added. The absorbance of the resulting solution was measured at a wavelength of 700 nm. A blank sample was prepared without the addition of extract to serve as a reference (Hassan *et al.*, 2022).

Gas Chromatography-Mass Spectroscopy (GC-MS) Analyses of Plant Extract: the extracts were soaked in methanol overnight and filtered. The GC-MS analysis GC-MS analysis of the extract was performed using an Agilent 5977B GC/MSD system coupled with Agilent 8860 auto-sampler, a Gas Chromatograph interfaced to a Mass Spectrometer (GC-MS) equipped with an Elite-5MS (5% diphenyl/95% dimethyl polysiloxane) fused a capillary column (30 × 0.25µm ID × 0.25 µm df) as described by (Saheed *et al.*, 2020).

Cell source and medium preparation: HepG2 cell lines were purchased from Cell Lines Service (CLS), Germany in 25 cm^3 culture flasks; both cells were with seeding density 1 x 10^4 cells/cm^2. The recommended medium regarding the composition of the growth medium for propagation of the cells is RPMI 1640 (9.4 g) supplemented with 1 % FBS (for maintenance medium, MM)/10 % FBS (for growth medium, GM), 2.0 g of $NaHCO_3$, 5.9 g of HEPES, and 1 % L-Glutamine in 1000 mL of autoclaved distilled water-medium was kept in the incubator for 24 hr. for sterility check (Chuen *et al.*, 2016).

Cell culturing and maintenance: Cells were grown in the supplemented medium in T25 and T75 flasks and maintained in a humidified chamber with 5 % CO_2 at 37 °C (incubator) until they reached a confluence of 75 %, medium was discarded, and cells were washed with PBS. Cells were detached using a 0.005 % Trypsin solution and they were re-suspended in medium and passed into new flasks (Kovalevich and Langford, 2013).

Harvesting, Viability Count, and Seeding of Cells: Floating HepG2 cells in the culture medium were

discarded, while adherent cells were detached using trypsin and harvested by resuspension in fresh culture medium. Cell viability was assessed using the trypan blue exclusion method. Briefly, 10 µL of the cell suspension was mixed with 10 µL of trypan blue solution, and 10 µL of the resulting mixture was loaded onto a haemocytometer. Viable cells were counted under a light microscope.

Cell concentration was calculated according to Equation (2), while percentage viability was determined using Equation (3).

$$Viability\ count\ (a/b) = \frac{AT * 2 * 10^4}{4} \quad (2)$$

$$\%Cell\ Viability = \left[\frac{AT}{AT + DT}\right] * 100 \quad (3)$$

Where: a/b represents the average cell counts from both haemocytometer chambers, AT denotes the total number of viable (unstained) cells, and DT denotes the total number of non-viable (trypan blue-stained) cells.

Following viability assessment, the harvested HepG2 cells were seeded into 96-well plates at a density of 1 × 10^5 cells/well and allowed to attach prior to treatment, as previously described (Chuen et al., 2016).

Dosing of Cells with Plant Extracts: After 24 hours, using Cisplatin as a positive control with a concentration range of 0 to 250 µg/mL, the cells were treated with the plant extracts with a concentration range of 0 to 5000 µg/mL and 0 to 2500 µg/mL respectively; each experiment was performed with two-fold dilution. After 48 hours, 10 µL of MTT solutions [1 % (w/v); Sigma-Aldrich] were added and incubation was done for 3 hrs, then DMSO was added to solubilize the formazan crystal. The optical density (OD) values were measured at 492 nm by an ELISA reader (Alsaweed, 2021).

Antidiabetic Effects of *Momordica charantia: Quantification of RNA:* HepG2 cells were cultured in low glucose RPMI-1640 with 10% FBS at 3.5 × 104 cells/mL in a 12-well plate. After 24 hours, the medium was removed and the cells were starved in serum-free medium for another 24 hours. The cells were then washed with PBS and treated with high glucose (HG, 30 mM) and high insulin (HI, 100 nM) to induce diabetes for 24 hours. Next, the cells were exposed to 200 µg/ml of (name of extract) for 24 hours, with positive controls (HG and HI; HG, HI and metformin, 2 mM) and negative control (NC). Total RNA was then isolated using Zymo RNA isolation kit following the manufacturer's instructions. DNA was digested with RNase-free DNase. Purified and concentrated RNA was analyzed by 1% agarose gel electrophoresis and quantified by NanoDrop.

Determination of the Gene expression using Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR): A two-step reverse transcription quantitative polymerase chain reaction (RT-qPCR) was conducted utilizing poly(dTs) and random hexamers as primers during the reverse transcription step. The cycling parameters for the first step included incubation at 70 °C for 5 minutes to linearize the RNA strand, followed by a single cycle at temperatures ranging from 37 °C to 42 °C for 45 minutes for reverse transcription. The subsequent steps involved incubation at 94 °C for 30 seconds to deactivate reverse transcriptase (RTase), and a final step at 4 °C for holding. The synthesized cDNA was then utilized in quantitative PCR in 0.2 µl tubes with Evagreen, using forward and reverse primers specific to the candidate and reference genes. The cycling parameters for the qPCR stage included an initiation step at 93 °C for 5 minutes, followed by 30-32 cycles at 94 °C for 20 seconds (denaturation), 55-63 °C for 30 seconds (annealing), and 72 °C for 30 seconds (elongation). The process concluded with a final elongation step at 72 °C for 10 minutes.

Statistical Analyses: Data obtained were analysed using Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (SPSS, Chicago IL, USA) and Microsoft Excel. Descriptive statistics (mean and standard deviation) and Analysis of Variance (one way) with means separated using the Duncan multiple range test and level of significance was considered as p = 0.05. The linear regression analysis was also performed to derive the equation used to estimate the $IC_{50.}$

RESULTS AND DISCUSSION

Phytochemical Composition of the Ethanol Extract of Momordica charantia plant: Qualitative analysis confirmed the presence of 11 major phytochemicals including flavonoids, tannins, phenols, alkaloids, saponins, terpenoids and reducing sugar as shown Table 1. The quantitative analysis of the phytochemicals as presented in Table 2 shows that tannin was found to be the most abundant phytochemical, with a concentration of 92.97±0.21 mg/100g, followed by phenol at 50.56±0.01 mg/100g and saponin at 56.87±0.01 mg/100g. Alkaloids were present at a concentration of 30.59±0.20 mg/100g, while reducing sugars measured 49.12±0.10 mg/100g. Cardiac glycosides were detected at a

concentration of 16.06±0.17 mg/100g, whereas anthraquinone exhibited the lowest concentration at 8.88±0.73 mg/100g. Flavonoids were found at a concentration of 38.98±0.91 mg/100g, and terpenoids at 15.86±0.19 mg/100g.

Table 1: qualitative analysis of the phytochemicals present in the ethanol extract of *Momordica charantia* plant

Phytochemical	Result
Tannin	+
Phenol	+
Phlobatannin	+
Alkaloid	+
Saponin	+
Flavonoid	+
Steroid	+
Anthraquinone	+
Terpenoid	+
Cardiac glycosides	+
Reducing sugar	+

Table 2: quantitative analysis of the phytochemicals presents the ethanol extract of *Momordica charantia* plant

Compounds	Average Composition (mg/100g)
Tannin	92.97 ± 0.21
Phenol	50.56 ± 0.01
Saponin	56.87 ± 0.01
Alkaloid	30.59 ± 0.20
Reducing sugar	49.12 ± 0.10
Cardiac glycosides	16.06 ± 0.17
Anthraquinone	8.88 ± 0.73
Flavonoid	38.98 ± 0.91
Terpenoid	15.86 ± 0.19

Each value is a mean ± S.E.M., n = 2. Values differ significantly with each other (P = 0.05)

Table 3 presents the chemical composition of the ethanol extract of *Momordica charantia* (bitter melon) plant using Gas Chromatography-Mass Spectrometry (GC-MS). Fifteen compounds were detected in the extract. It shows that most of the compounds have retention times in a relatively close range (9.959 -15.636 min). n-Hexadecanoic acid has the highest peak area percentage at 42.19%, indicating it is the most abundant compound in the extract. Epianastrephin has the lowest peak area percentage at 0.85%. Most compounds have a high-quality percentage, ranging from 94% to 99%, which indicates the high purity of these compounds in the extract. However, 6,10-dimethyl-2-Undecanone) has the lowest quality percentage at 49%.

Antioxidant Activities of Ethanol Extract of Momordica charantia Plant: The antioxidant potential of the extract at various concentrations is illustrated in table 5. The extract's iron (III) reducing power, consistently rises with escalating concentration. It was observed that the extract exhibits its weakest reducing power at 25 µg/mL (0.124) and its highest at 100 µg/mL (0.544), demonstrating an IC50 of 78.40 µg/mL while ascorbic acid had higher IC50 of 96.15 µg/mL. The extract's DPPH scavenging activity shows an upward trend with increasing concentration. The extract displays its least scavenging activity at 25 µg/mL (26.72%) and its greatest at 100 µg/mL (76.38%), yielding an IC50 of 63.18 µg/mL while ascorbic acid had a lower IC50 of 30.36 µg/mL. The extract's nitric oxide (NO) scavenging activity, which also exhibits a positive correlation with concentration. At 25 µg/mL, the extract demonstrates the lowest scavenging activity (28.74%), while at 100 µg/mL, it achieves the highest (83.61%), with an IC_{50} of 42.78 µg/mL. while ascorbic acid had a lower IC_{50} of 46.97 µg/mL.

Table 3: chemical composition of ethanol extract of *Momordica charantia* plant using GC-MS

Peak Number	Compound	Molecular formula	Retention Time	Peak Area (%)	Quality (%)
1	(E)-2-Tetradecene	$C_{14}H_{28}$	9.959	0.91	97
2	Neophytadiene	$C_{20}H_{36}$	12.208	11.18	99
3	6,10-dimethyl-2-Undecanone	$C_{13}H_{26}O$	12.294	1.06	49
4	1-Hexadecyne	$C_{16}H_{32}$	12.414	2.01	70
5	3,7,11,15-Tetramethyl-2-hexadecenol	$C_{21}H_{42}O$	12.574	4.62	87
6	Hexadecanoic acid, methyl ester	$C_{19}H_{38}O_2$	12.958	5.91	99
7	n-Hexadecanoic acid	$C_{16}H_{32}O_2$	13.381	42.19	99
8	7,10,13-Hexadecatrienoic acid, methyl ester	$C_{20}H_{34}O_2$	14.371	2.92	94
9	Phytol	$C_{20}H_{40}O_2$	14.451	3.97	91
10	Methyl stearate	$C_{19}H_{38}O_2$	14.531	1.95	98
11	(Z,Z)-9,12-Octadecadienoic acid	$C_{18}H_{34}O_2$	14.709	4.08	98
12	(Z,Z,Z)-9,12,15-Octadecatrienoic acid	$C_{18}H_{26}O_4$	14.749	9.14	98
13	Octadecanoic acid	$C_{18}H_{36}O_2$	14.875	9.75	99
14	13-Oxabicyclo[10.1.0]tridecane	$C_{11}H_{18}O$	15.001	0.85	95
15	Epianastrephin, (-)	$C_{12}H_{18}O_4$	15.636	15.636	47

Cytotoxicity of Ethanol Extract of Momordica charantia plant on Normal HepG2 Cell Line: The cytotoxicity assessment using the MTT assay was conducted on the normal HepG2 cell line following a 48-hour exposure to the test extracts. Notably, the half maximal inhibitory Concentration (IC_{50}) for the ethanol extract of *Momordica charantia* plant was determined to be 6183.52 µg/mL. In comparison, cisplatin exhibited an IC_{50} value of 171.37 µg/mL (Table 4).

Table 4: half maximal inhibitory concentration (ic_{50}) of ethanol extract of *Momordica charantia* plant and cisplatin on Hep G2 cell line

Treatments	IC_{50} (µg/mL)
Momordica charantia extract	6183.52
Cisplatin	171.37

Table 5: in-vitro antioxidant assays of ethanol extract of *Momordica charantia* plant

Antioxidant assay	IC_{50} (µg/mL)	Ascorbic acid (µg/mL)
(DPPH) Scavenging Activity Assay	63.18	30.36
Nitric Oxide Inhibition Assay	42.78	46.97
Reducing Power Assay	78.40	96.15

Gene Expression Assessment: Table 6 summarizes the RNA concentration and purity indices of HepG2 cells under different treatment conditions in the insulin resistance model. The *Momordica charantia* extract–treated group (7.8 ng/mL) showed acceptable RNA purity, with A260/280 and A260/230 ratios of 2.00 and 1.83, respectively. The insulin-resistant model alone (13.4 ng/mL) exhibited lower purity, with ratios of 1.87 (A260/280) and 0.22 (A260/230). Cells treated with both the insulin-resistant model and metformin (32.7 ng/mL) demonstrated improved RNA quality, with ratios of 2.01 and 1.88, while the negative control (31.9 ng/mL) showed an A260/280 ratio of 2.02 and an A260/230 ratio of 0.35. Table 7 presents the effects of the ethanol extract of *Momordica charantia* on gene expression in insulin-resistant HepG2 cells. The extract did not alter the quantification cycle (Cq) value of GHPD (28.49 ± 1.87) relative to the insulin-resistant group, although this value remained higher than those observed in the metformin-treated and negative control groups. In contrast, treatment with the plant extract reduced the Cq values of AKT (30.38 ± 0.89) and IRS (31.53 ± 0.65) to levels lower than all control groups. The Cq value of PIP3 (30.41 ± 1.34) was also decreased by the extract but remained higher than that of the negative control. Comparative analysis of relative mRNA expression revealed a significant downregulation of all assessed genes, with fold changes ranging from approximately 0.68 to 0.25. Specifically, AKT, IRS, and PIP3 expression levels were reduced by 0.68, 0.12, and 0.25-fold, respectively.

Table 6: concentrations of the RNA of the insulin resistance cell model (HepG2 cell)

Treatment	Concentration (ng/ml)	Absorbance at 260/280	Absorbance at 260/230
Momordica charantia extract	7.8	2.00±1.02	1.83±0.03
IRM	13.4	1.87±0.10	0.22±1.04
IRM + Metformin	32.7	2.01±1.04	1.88±2.07
NC	31.9	2.02±1.05	0.35±0.02

Each value is a mean ± S.E.M., n = 2. Values differ significantly with each other (P = 0.05)

N.B: *EXTRACT = Momordica charantia extract; IRM = Insulin Resistant Model; IRM+Met = Insulin Resistant Model + metformin; NC = Negative Control*

Table 7: effect of *Momordica charantia* ethanol extract on the gene expression in insulin resistance cell model (HepG2 cell)

Well	Content	Treatment	Quantification Cycle (Cq)			
			GHPD	AKT	IRS	PIP3
A04	Unkn	Extract	28.49±1.87	30.38±0.89	31.53±0.65	30.41±1.34
A10	Neg Ctrl	IRM	27.32±2.47	28.66±2.22	27.30±0.47	27.28±3.52
A11	Pos Ctrl	IRM+Met	29.49±0.05	30.48±3.20	28.66±1.25	26.32±3.36
A12	Neg Ctrl	NC	29.37±3.60	28.09±0.87	27.99±0.17	25.96±8.24

Each value is a mean ± S.E.M., n = 2. Values differ significantly with each other (P = 0.05) in all the groups.

The ethanol extract of *Momordica charantia* analyzed in this study contained eleven phytochemical constituents: tannin, phenol, phlobatannin, alkaloid, saponin, flavonoid, steroid, anthraquinone, terpenoid, cardiac glycosides, and reducing sugar. Quantitative analysis revealed tannin as the most abundant constituent, with a concentration of 92.97 ± 0.21 mg/100 g. Cardiac glycosides were present at 16.06 ± 0.17 mg/100 g, while anthraquinone recorded the lowest concentration at 8.88 ± 0.73 mg/100 g. Flavonoids and terpenoids were detected at concentrations of 38.98 ± 0.91 mg/100 g and 15.86 ± 0.19 mg/100 g, respectively. This phytochemical composition underscores the ethanol extract of the *Momordica charantia* plant as a reservoir of diverse bioactive compounds. These findings lend credence to the plant's historical use in traditional medicine for a wide array of ailments (Ahmad *et al.*, 2016). Furthermore, the rich phytochemical profile indicates the potential pharmacological versatility of the extract, with implications for various therapeutic applications, including antidiabetic and antioxidant properties, aligning with the established biological activities associated with these phytochemicals (Baek *et al.*, 2018; Chang *et al.*, 2017). These findings align with the report made by de Oliveira *et al.* (2019), Oloruntola *et al.* (2021) and Oyelere *et al.* (2022) that *Momordica charantia* contains the phytochemicals found in this study. However, Oloruntola *et al.* (2021)

reported flavonoid the major phytochemicals present in leaf extract of the plant.

Table 8: relative fold change

	AKT	IRS	PIP3
SD	0.684	0.120	0.257
NC	1	1	1
IRM	1.273	1.758	8.730
IRM +metformin	6.101	2.570	10.298

GC–MS analysis of the ethanol extract of *Momordica charantia* revealed the presence of fifteen distinct compounds with varied chemical structures and properties. Among these, n-Hexadecanoic acid was the most abundant constituent, exhibiting the highest peak area percentage (42.19%), indicating its dominance in the extract's chemical composition. This was followed by Neophytadiene (11.18%) and Octadecanoic acid (9.75%). In contrast, Epianastrephin was the least abundant compound, with a peak area percentage of 0.85%. Overall, the results highlight considerable variability in the abundance of the identified compounds and provide insight into the chemical profile and major constituents of the ethanol extract. Comparison with previous studies confirms that *Momordica charantia* is rich in diverse phytochemicals, consistent with reports by Parkash *et al.,* (2017), Murakami *et al.,* (2016), and Ahmad *et al.,* (2016). These studies documented compounds such as charantin, charine, cucurbitacins, diosgenin, and several organic acids including galacturonic, gentisic, lauric, linoleic, and linolenic acids. The phytochemicals identified in the present study showed partial overlap with earlier findings, with observed variations likely attributable to differences in extraction methods and analytical techniques. Additionally, antioxidant evaluation demonstrated that the extract possesses both ferric (Fe^{3+}) reducing and free radical scavenging activities. Antioxidant efficacy is largely dependent on the presence of reductants capable of interrupting free radical chain reactions through hydrogen atom donation (Anigboro *et al.,* 2019). In this study, such reductants facilitated the reduction of the Fe^{3+}/ferricyanide complex to its ferrous form, with reducing power increasing in a concentration-dependent manner. At 100 µg/mL, the extract exhibited a reduction activity of 0.6135 and an IC_{50} value of 78.40 µg/mL, which was lower than that of ascorbic acid (96.15 µg/mL). These findings are in agreement with reports by Ibisanmi and Aribisala (2022) and Perumal *et al.,* (2021) on the ferric reducing potential of *Momordica charantia*. The study further evaluated the DPPH free radical scavenging activity of the extract, using 2,2-diphenyl-1-picrylhydrazyl, a stable radical commonly employed to assess antioxidant capacity due to its ability to accept electrons or hydrogen atoms and form a stable diamagnetic molecule (Hassan *et al.,* 2022). The results demonstrated a concentration-dependent increase in DPPH scavenging activity. At 100 µg/mL, the extract exhibited a high scavenging activity of 76.38%, with an IC_{50} value of 63.18 µg/mL. In comparison, ascorbic acid showed a lower IC_{50} value of 30.36 µg/mL, indicating a relatively stronger radical scavenging efficiency. Nonetheless, the findings confirm the extract's effective free radical scavenging potential and are consistent with earlier reports by Ibisanmi and Aribisala (2022) and Perumal *et al.,* (2021), which documented the DPPH scavenging ability of *Momordica charantia* extracts. Nitric oxide (NO) radical is a versatile molecule that plays a pivotal role in a multitude of biological processes. Its interactions are known to extend to reactions with the superoxide radica, forming peroxynitrite radicals that can have detrimental effects on biomolecules and contribute to inflammatory processes (Omeje *et al.*, 2019). Given these implications, the capacity of the plant extract to scavenge NO is of significant interest, holding potential advantages for the prevention and treatment of related ailments. In the present study, the NO scavenging activity of the plant extract increased in a concentration-dependent manner. At 100 µg/mL, the extract demonstrated a high NO scavenging activity of 83.61%, with an IC_{50} value of 42.78 µg/mL. In comparison, ascorbic acid exhibited a slightly lower IC_{50} value of 46.97 µg/mL. These results indicate that the extract is effective in neutralizing NO radicals, although ascorbic acid showed marginally greater scavenging efficiency. The findings are consistent with previous reports by Ibisanmi and Aribisala (2022), which also documented the NO scavenging potential of *Momordica charantia* extracts. The current study also demonstrated that the ethanol extract of *Momordica charantia* exerted a measurable cytotoxic effect on the HepG2 cell line, a widely used model of human liver cancer. The IC_{50} value of the extract was 6183.52 µg/mL, indicating inhibitory activity against HepG2 cell proliferation. In comparison, the standard anticancer drug cisplatin showed a markedly lower IC_{50} value of 171.37 µg/mL, reflecting its substantially higher cytotoxic efficacy. Although the plant extract was less potent than cisplatin, these findings confirm its cytotoxic potential. This observation is consistent with previous studies, including Basaran *et al.,* (2017), who reported cytotoxic effects of *Momordica charantia* on androgen-dependent (LnCAP) and androgen-independent (PC-3) prostate cancer cell lines, as well as Houacine *et al.,* (2021), who demonstrated the cytotoxic activity of ethanol extracts of *Momordica*

charantia against MCF-10A, MCF-7, and MDA-MB-231 breast cancer cell lines.

It was further discovered that the *Momordica charantia* extract exhibits antidiabetic potential through modulation of gene expression in HepG2 cells, a commonly used model of insulin resistance. Treatment with the extract enhanced insulin sensitivity by reducing the Cq values of key insulin signaling mediators, AKT and IRS. In addition, the extract increased the level of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), a lipid signaling molecule involved in the activation of AKT and downstream insulin-responsive pathways. The extract also suppressed the expression of GHPD, an enzyme associated with the conversion of glucose to glycogen. Comparative analysis of relative mRNA fold changes among extract-treated, metformin-treated, and control cells showed a significant down regulation of gene expression, ranging from approximately 0.68 - 0.25-fold. Specifically, AKT, IRS, and PIP3 expression levels were reduced by 0.68, 0.12, and 0.25-fold, respectively, highlighting the extract's modulatory effect on genes central to insulin signalling and glucose metabolism. However, the extract was not as effective as metformin, a common antidiabetic drug, which indicates that the extract had a different mode of action. The extract also failed to normalize the expression of the genes to the level of the negative control, which suggests that the extract could not fully reverse the insulin resistance in HepG2 cells. This agrees with the report made by Elekofehinti (2022) and Saxena *et al.,* (2022) that *Momordica charantia* could modulate and down regulates diabetic gene related expressions.

Conclusion: This study highlights the multifaceted pharmacological potential of the ethanol extract of *Momordica charantia*, demonstrating a rich phytochemical composition dominated by saponins, tannins, and phenols, alongside fifteen GC–MS–identified compounds with n-hexadecanoic acid as the major constituent. The extract exhibited notable antioxidant activity through ferric reducing power and effective scavenging of DPPH and nitric oxide radicals, indicating strong capacity to mitigate oxidative stress and inflammation. In addition, it showed significant cytotoxic and antidiabetic effects in HepG2 cells, likely attributable to its bioactive and antioxidant constituents. Overall, the study achieves a comprehensive biochemical and cellular evaluation of *M. charantia*, supporting its potential as a complementary therapeutic agent for diabetes management. It is recommended that further in vivo and clinical studies be conducted to validate efficacy and safety, while future research should focus on isolating specific active compounds and elucidating their molecular mechanisms of action.

DECLARATIONS

Ethical Approval: This study did not involve human participants or animal experimentation and therefore did not require formal ethical approval. All procedures involving data handling and analysis were conducted responsibly and in accordance with standard academic and institutional guidelines.

Disclaimer (Artificial Intelligence): Authors hereby declare that no generative Artificial Intelligence (AI) technologies such as Large Language Models (ChatGPT, COPILOT, XLNet, Ernie 3.0 Titan etc) and text to-image generators have been used during writing or editing of this manuscript.

Declaration of Conflict of Interest: The authors declare that no known conflict of interest or personal relationships that have influence the work reported in this paper.

Declaration of Data Availability: Data are available upon request from the corresponding author

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