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Antioxidant activity of *Brachiaria sabia* and *Brachiaria marandu* and Molecular Docking of Constituents targeting Insulin-like Growth Factor 1 Receptor (IGF-1R) for cancer treatment

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Abstract

The methanol extracts of *Brachiaria sabia,* and *Brachiaria marandu* leaves were evaluated for its ability to scavenge free radicals, reduce ferric iron, and function as an iron chelator. The extracts were subjected to HPLC analysis. The two *Brachiaria* species possessed strong antioxidant activity, with *B. marandu* had a higher percentage (%) of phenolic content than *Brachiaria gayana*. *In silico* studies revealed that the two *Brachiaria* grasses tested enhanced insulin-like growth receptor factor-1 receptors (IGF-1R). Quercetin, which is consistent compound in the two grasses, had highest binding affinity to insulin-like growth factor-1 receptors with value of -40.5971. This study therefore reveals that *Brachiaria sabia,* and *Brachiaria marandu* are good antioxidant and Quercetin, a constituent of *Brachiaria* grasses, binds to insulin-like growth factor-1 receptors (IGF-1R) which plays an important role in cancer cell proliferation. *In vivo* and *in vitro* research are also necessary to validate this in silico result.

Keywords: *Brachiaria sabia*, *Brachiaria marandu*, Cancer, Antioxidants, Insulin-like growth factor-1 receptors

Introduction

An estimated 11.5 million deaths from cancer are predicted by 2030, making it the second greatest cause of mortality worldwide [1]. Based on research conducted by Bray et al. [2], men are more likely than women to get colorectal, lung, liver, prostate, stomach, and cervical cancers among the 36 distinct forms of cancer. Some conventional and modern techniques used to treat cancer include radiation treatment, chemotherapy, and surgery [3]. Numerous disadvantages of these techniques include toxicity and adverse reactions associated with the use of conventional chemicals in cancer treatment [4]. The discovery of novel, efficient drugs with minimal side effects is necessary for the prevention and treatment of this illness due to the inefficiency of conventional chemotherapeutic approaches [5].

The tyrosine kinase receptor known as the insulin-like growth factor-1 receptor (IGF-1R) is believed to have an impact on the development of several malignancies [6]. Through this receptor, the insulin-like polypeptide protein hormone IGF-1 mediates its activities [7] IGF-1 is essential for development and continues to have anabolic effects throughout adulthood that extend to the control of cancer and free radicals. It has been discovered that IGF-IR is markedly overexpressed in a large number of human solid tumours, including sarcomas, hepatocellular carcinoma, pancreatic, ovarian, and gastrointestinal cancers, as well as breast, non-small cell lung, and prostate cancer [8-11]. After ligand binding, IGF-1R can initiate the Ras/Raf/MEK/MAPK and PI3K/AKT/mTOR signalling pathways. These pathways then activate several transcription factors, including AP-1, CREB, and ELK-1, to affect angiogenesis, invasion, motility, and cell proliferation [2,13]. Furthermore, accumulating evidence indicates that IGF-1R is essential for tumour growth and plays a role in the critical stages of the metastatic cascade [14,15]. Thus, one of the most sought-after targets for cancer therapy strategies is IGF-1R [16,17].

Antioxidants are abundant in botanicals. Antioxidants are substances that can prevent or lessen the harm that these unstable chemicals do to cells. In addition, antioxidants act as synergists, metal-chelating agents, hydrogen donors, electron donors, peroxide decomposers, enzyme inhibitors, and radical scavengers. *Brachiaria sabia* and *Brachiaria marandu* was shown to contain alkaloid [18]. These grasses showed moderate levels of terpenoids and flavonoids. Tannins and saponins, however, were absent. This outcome is consistent with a study conducted by Ogunlakin *et al*. [19], which found that alkaloids, terpenoids, and flavonoids found in Brachiaria grasses may be advantageous to the growth and production of animals who eat them. *Brachiaria marandu* had the highest total phenolic content when compared to *Brachiaria sabia* [18]. The aim of this study is to evaluate the antioxidant and anticancer activity of *Brachiaria sabia* and *Brachiaria marandu* via Molecular Docking of Constituents targeting Insulin Growth Factor 1 Receptor (IGF-1R).

2. Materials and methods

2.1. Plants collection and Extraction

On May 31, 2022, *Brachiaria sabia* and *Brachiaria marandu* were collected from the dairy farm at Bowen University in Iwo, Osun state. The grasses were prepared for extraction by being air dried, pulverized into a powder using an electric grinder, weighed, and kept in dry, clean beakers. 500 g of each powdered sample were extracted with methanol. At 40°C, concentrated filtrates were concentrated in a vacuum using a Stuart-RE300DB rotary evaporator. The extracts were stored in the refrigerator for further use.

2.2. Antioxidant parameters

2.2.1 Iron-chelation antioxidant assay

The ability of the methanolic extracts of *Brachiaria sabia* and *Brachiaria marandu* to chelate ferrous ions was evaluated using a slightly modified procedure of the Ajiboye et al. [20]. This test evaluates the capacity to chelate ferrous ions by stopping Fe^{2+} from binding to ferrozine and forming a vividly colored complex.

2.2.2 OH radical scavenging ability

The ability of the methanolic extracts of *Brachiaria sabia* and *Brachiaria marandu* to scavenge hydroxyl radicals was assessed using the methods reported by Ogunlakin *et al*. [21], with a few minor modifications.

2.2.3 Ferric-reducing antioxidant power (FRAP)

The ferric-reducing antioxidant capability was determined by measuring the capacity of the methanolic extract of *Brachiaria sabia* and *Brachiaria marandu* to change ferric ions (Fe^{2+}) into ferrous ions (Fe^{3+}). The initial plan for this surgery was changed. It was said to be the only assay that measures antioxidants (or reductants) in a sample directly, in contrast to other methods assessing the suppression of free radicals [21].

2.2.4 DPPH radical scavenging activity

By slightly modifying the procedure outlined by Ogunlakin *et al*. [21], the DPPH radical was used to assess the free radical scavenging ability of the methanol extract of *Brachiaria sabia* and *Brachiaria marandu*.

High-Performance Liquid Chromatography (HPLC) analysis

Using Ayeni et al.'s [18] technique, High-Performance Liquid Chromatography (HPLC) analysis was performed to determine the phytochemicals present in the methanol extracts of *Brachiaria sabia* and *Brachiaria marandu*. After a few adjustments, the composition gradient looked like this: 5% of methanol (B) for the first two minutes, after which the percentage was adjusted to produce different values between 10 and 60 minutes, spaced out by ten minutes. Water with 2% acetic acid (A) and methanol (B) was the mobile phase.

2.5 *In silico* studies

2.5.1 Ligand preparation

To prepare ligands, Schrodinger Suite 2020-4's LigPrep module was utilized. The force field known as OPLS_2005 (Optimised Potentials for Liquid Simulations) was utilized to minimize energy. LigPrep converted 2D structures into 3D structures by including hydrogens, accounting for bond lengths and angles, and selecting the conformers' structure that showed the lowest conformational energy. Accurate tautomers, chirality, stereochemistry, and ring conformations are prerequisites for these steps. Using the Epik ionization tool, the ionization state was established at a pH range of 7.0 ± 2.0 [22].

2.5.2 Target structure preparation

In this study, the insulin-like growth factor-1 receptor's crystal structure in the selected Brachiaria species was recovered using the protein data bank (PDB) 7E3H [23]. Using the Maestro v12.6 protein preparation wizard (part of the Schrodinger Suite 2020-4), the protein was made, and the bond order was modified. Furthermore, PROPKA provided the hydrogen atoms at pH 7.0 following the removal of the crystallographic water molecules. Docking was done with the OPLS 2005 force field, constrained minimization with an RMSD of 0.30 being the default, and Epik was also used to construct het states [22].

2.5.3 Receptor grid generation

By enclosing a box around the centroid of the co-crystallized ligands associated with each receptor (the binding pocket), the receptor grid generation module built the grid boxes for each receptor. This technique ensures the docked ligands stay inside the enclosing box by blocking non-specific binding. The co-crystallized ligands of 7E3H were selected to define the grid box to preserve the center of each docked ligand with the same dimensions as the binding pocket [24].

2.5.4 Molecular docking

The prepared and minimized compounds were docked into the receptor's binding region in this work using the XP (Extra-Precision algorithm) docking technique, and the interactions between the ligands and receptor were analyzed. The XP views the receptor as stiff and the ligand sampling as flexible. The OPLS_2005 force field was used in the docking calculations. The 2D interactions of the complexes were investigated using the Schrodinger suite's ligand interaction diagram module [25].

3. Results

3.1 Antioxidant activity and HPLC analysis

Ascorbic acid was utilized as the control in Figure 1, however, *Brachiaria sabia* and *Brachiaria marandu* showed increased capacity to scavenge DPPH. Figure 2 shows *Brachiaria marandu* has a higher ferric-reducing antioxidant capacity than *Brachiaria sabia*. Both plant extracts reduced ferric ions than the control (ascorbic acid). *Brachiaria sabia* has a greater capacity to scavenge hydroxyl radicals than *Brachiaria marandu*, however, it still has lower values than the ascorbic acid standard (Figure 3). The concentration-dependent increase in chelating iron was observed in the methanol extracts of *Brachiaria sabia* and *Brachiaria marandu*. However, the iron chelating capability of these plants was lower than the benchmark, ascorbic acid (Figure 4). The HPLC phytochemical analyses of *B. sabia* and *B. marandu* are shown in Figures 5 and 6, which indicate that *B. marandu* has more embedded phenolic compounds than *B. sabia*. Tables 1 and 2 display the percentage (%) content of phenolic compounds for the two Brachiaria grasses. The results indicate that *B. marandu* had a higher percentage (%) of phenolic content than the other grass.

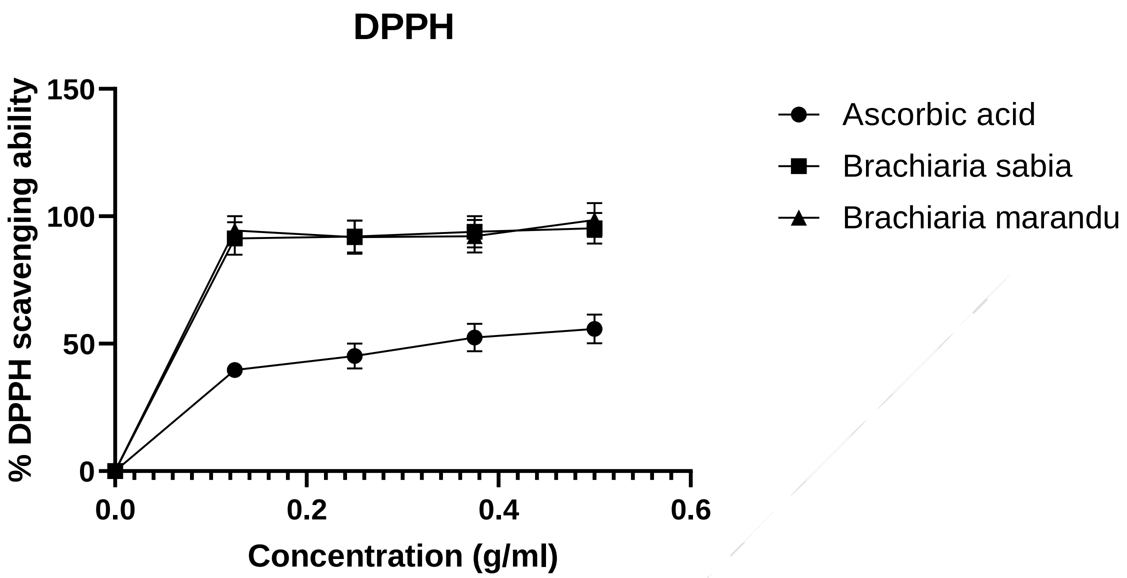


Figure 1: Percentage DPPH scavenging ability of *Brachiaria sabia* and *Brachiaria marandu*

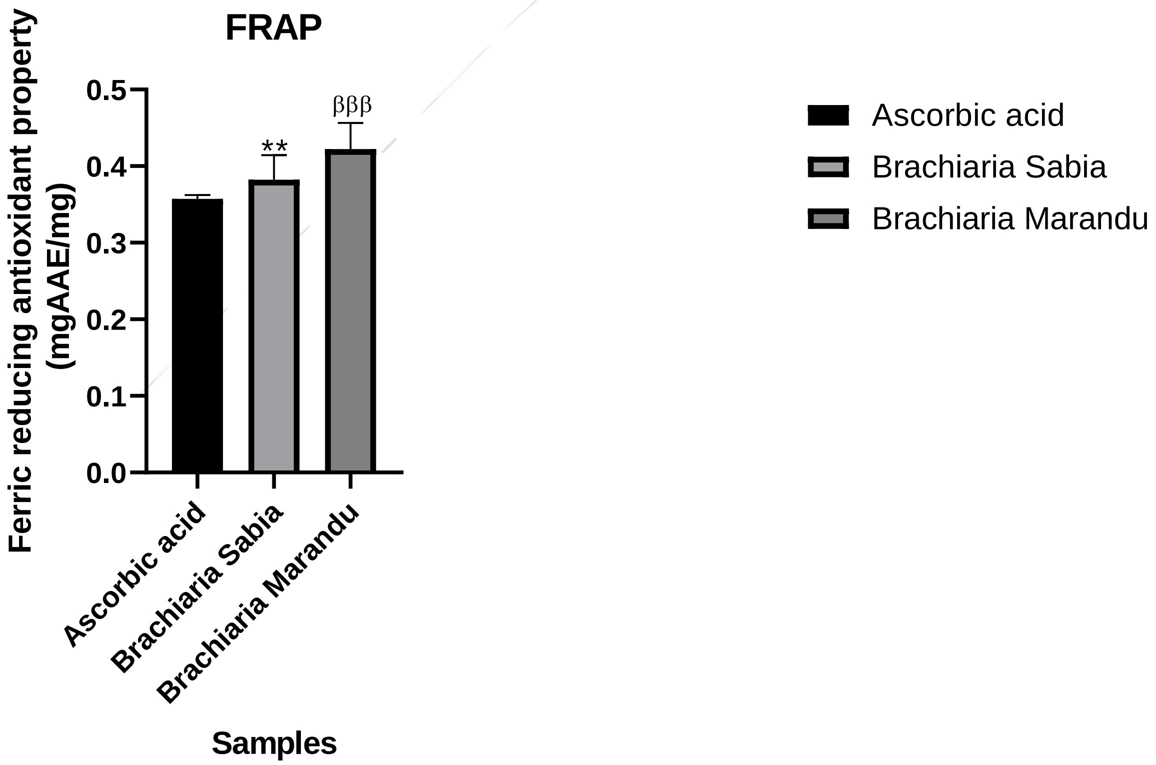


Figure 2: Ferric reducing property of *Brachiaria sabia* and *Brachiaria marandu*

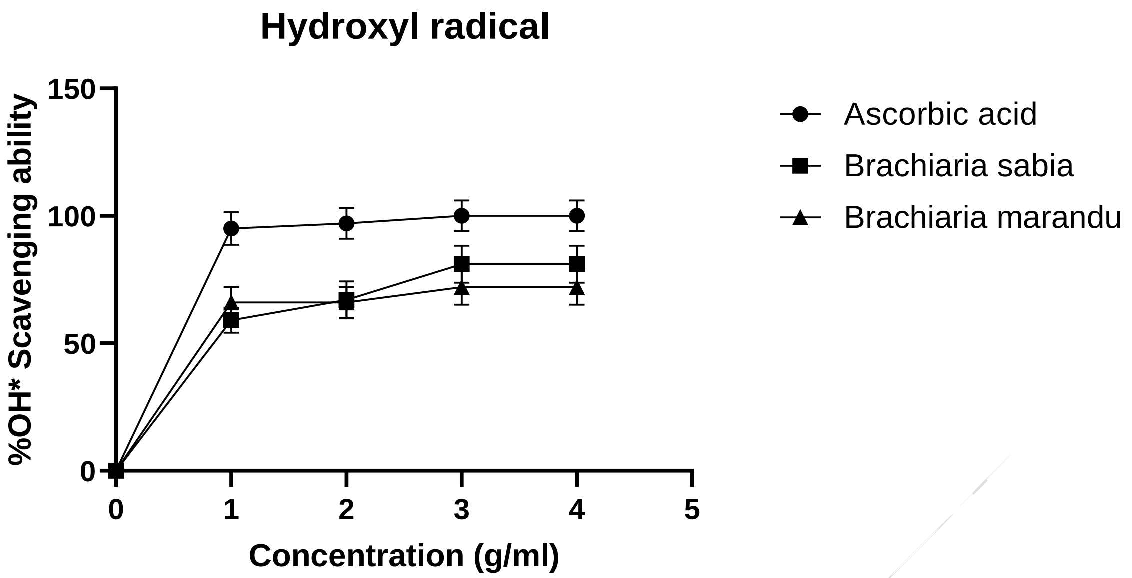


Figure 3: Percentage hydroxyl radical scavenging ability of *Brachiaria sabia* and *Brachiaria marandu.*

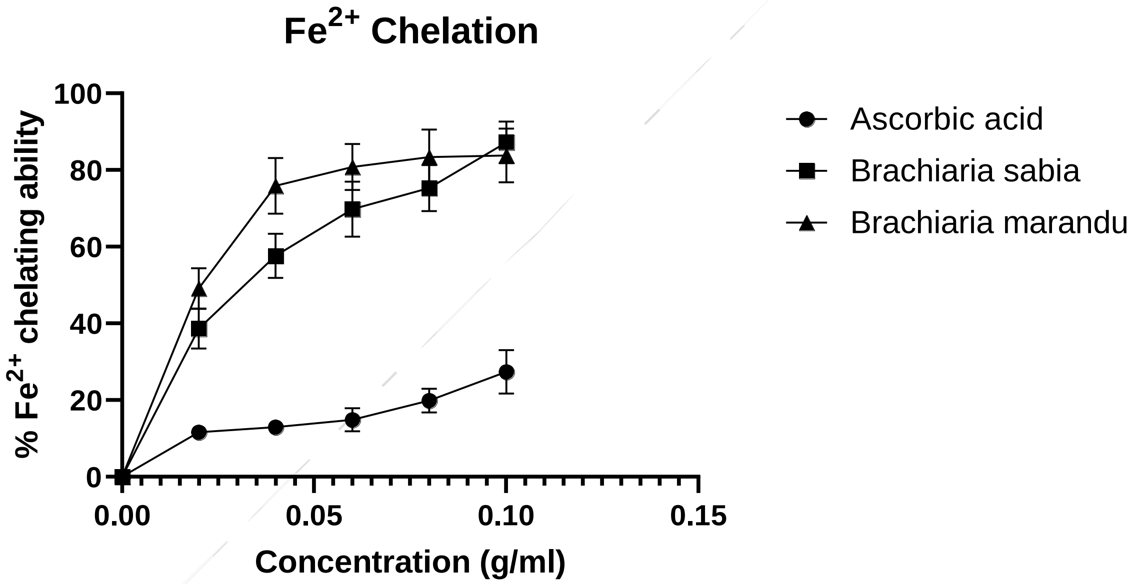


Figure 4: Percentage Iron chelating ability in *Brachiaria sabia* and *Brachiaria marandu.*

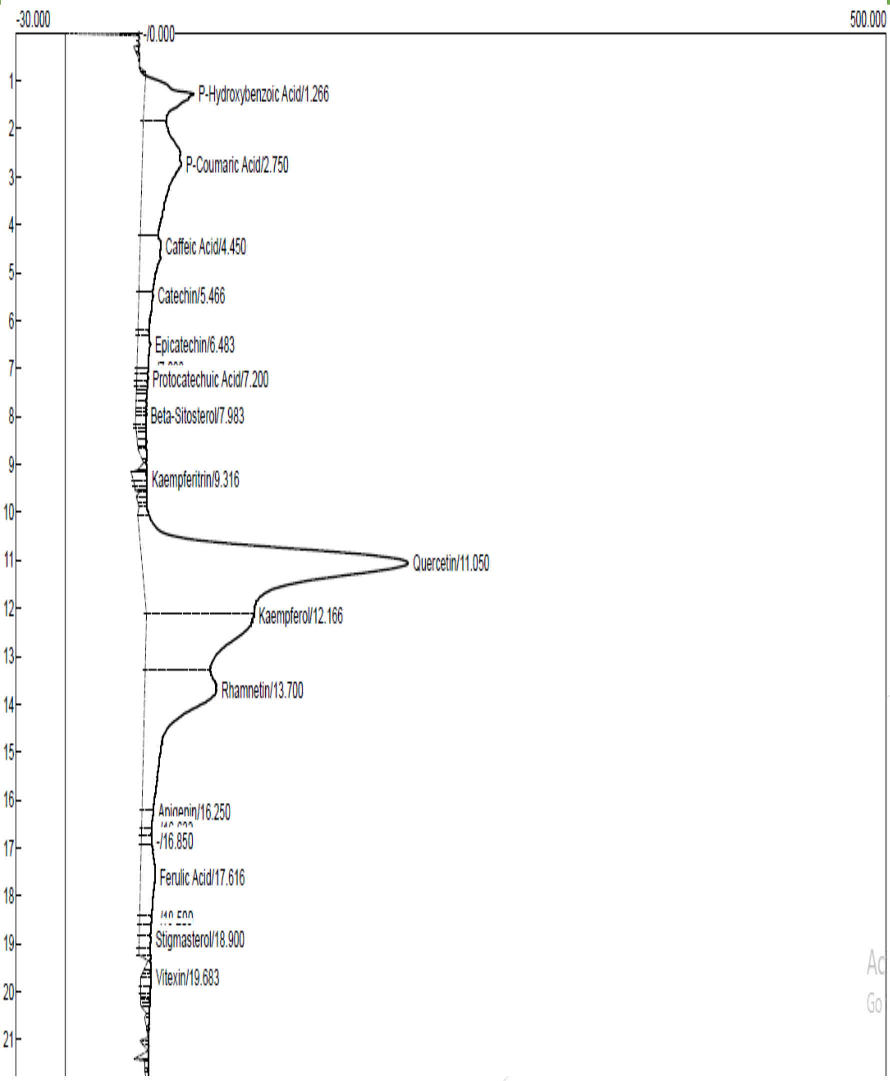


Figure 5: Phytochemical screening of *Brachiaria sabia*

Table 1: Phenolic compounds and % content of *Brachiaria sabia*

Phenolic Compounds	**% Content**
Para-hydroxy-benzoic acid	4.26
Para-hydroxy- coumaric acid	10.64
Caffeic acid	3.39
Catechin	1.61
Epicatechin	1.20
Protocatechuic acid	0.26
Kaempferitin	0.42
Quercetin	42.13
Kaempferol	16.23
Rhamnetin	14.93
Apigenin	0.62
Ferulic acid	3.12
Stigmastrerol	0.48
Vitexin	0.33

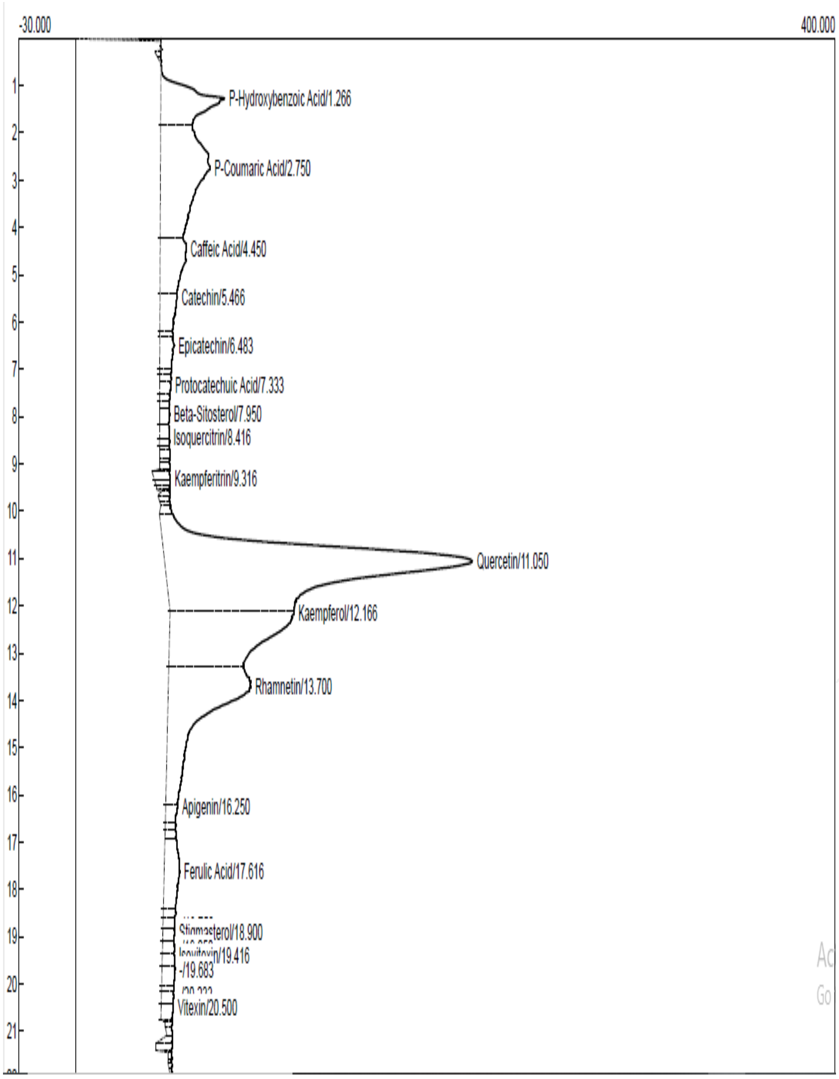


Figure 6: Phytochemical screening of *Brachiaria marandu*

Table 2: Phenolic compounds and % content of *Brachiaria marandu*

Phenolic Compounds	% Content
Para-hydroxy-benzoic acid	5.07
Para-hydroxy- coumaric acid	11.56
Caffeic acid	3.56
Catechin	1.62
Epicatechin	1.12
Protocatechuic acid	0.38
Protocatechuic acid	0.36
Kaempferitin	0.41
Quercetin	40.92
Kaempferol	15.17
Rhamnetin	14.18
Apigenin	0.54

Ferulic acid	2.75
Stigmastrerol	0.41
Isovitexin	0.44
Vitexin	0.50

3.2 *In silico* study

Brachiaria sabia has a greater capacity to scavenge hydroxyl radicals than *Brachiaria marandu*, however, it still has lower values than the ascorbic acid standard (Figure 3). The concentration-dependent increase in chelating iron was observed in the methanol extracts of *Brachiaria sabia* and *Brachiaria marandu*. However, the iron chelating capability of these plants was lower than the benchmark, ascorbic acid (Figure 4). Figure 6 shows the structure of insulin-like growth factor-1 receptors. Table 6 displays the docking scores and MM-GBSA post-grid docking. Quercetin, had the greatest docking score, followed by Kaempferol. It was discovered that in comparison to other bioactive compounds, quercetin, kaempferol, and rhamnetin showed significant binding affinities to insulin-like growth factor-1 receptors (Figure 8).

Table 3: Consistent compounds in *B. sabia* and *B. marandu*

Molecule	Name	Smile
Compound 1	Para-hydroxy-benzoic acid	C1=CC(=CC=C1C(=O)O)O
Compound 2	Para-hydroxy-coumaric acid	C1C=C(C=CC1(O)O)/C=C/C(=O)O
Compound 3	Caffeic acid	C1=CC(=C(C=C1/C=C/C(=O)O)O)O
Compound 4	Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Compound 5	Kaempferol	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Compound 6	Rhamnetin	COC1=CC(=C2C(=C1)OC(=C(C2=O)O)C3=CC(=C(C=C3)O)O)O
Compound 7	Ferulic acid	COC1=C(C=CC(=C1)/C=C/C(=O)O)O

TARGET **SWISS-MODEL: Q05688 (IGF1R_BOVIN) Bos taurus (Bovine)**

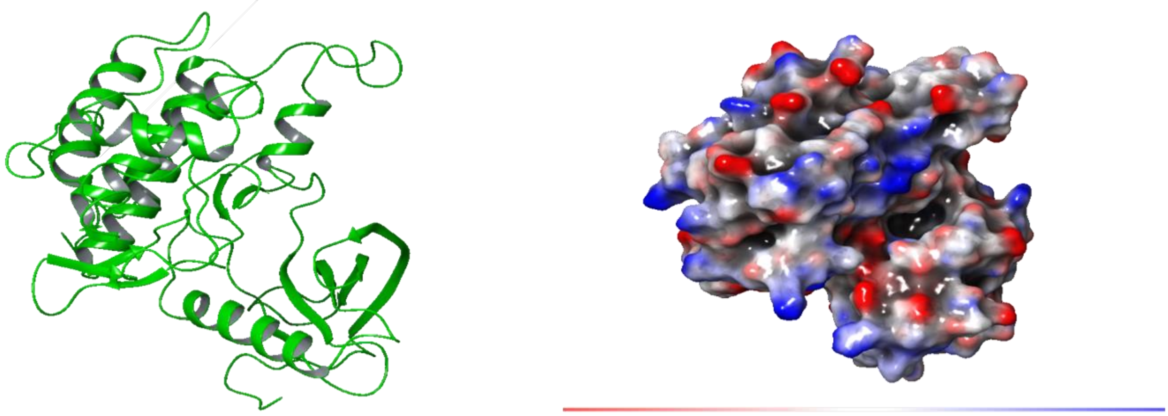
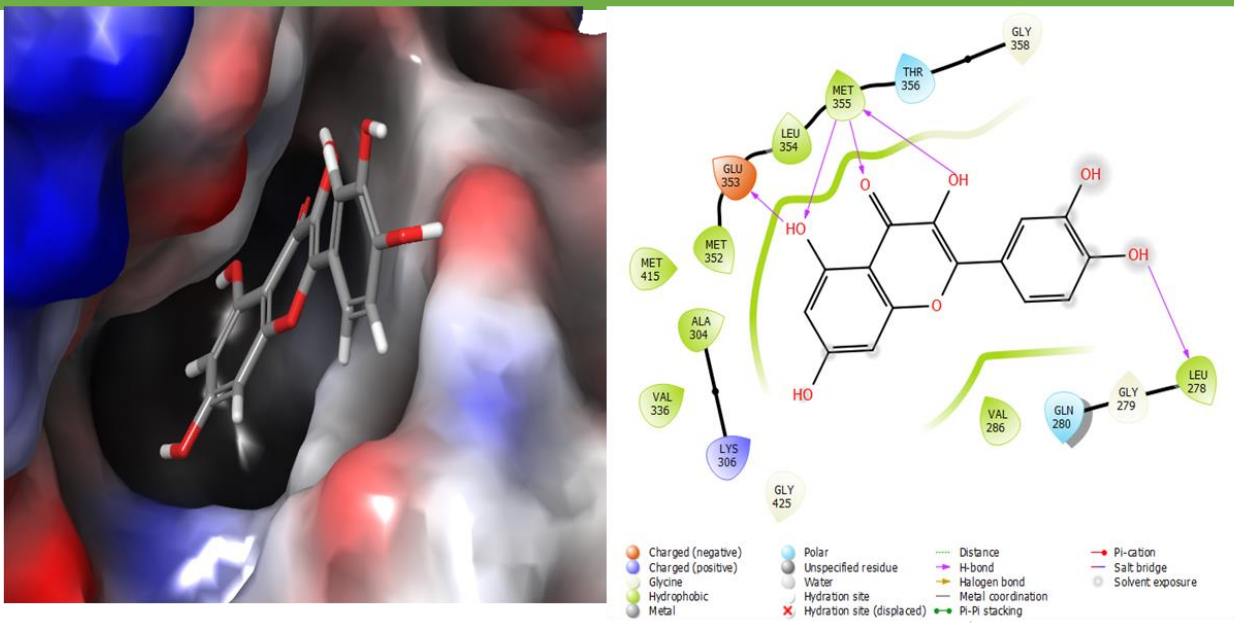


Figure 7: Structure of Insulin-like Growth Factor -1 Receptor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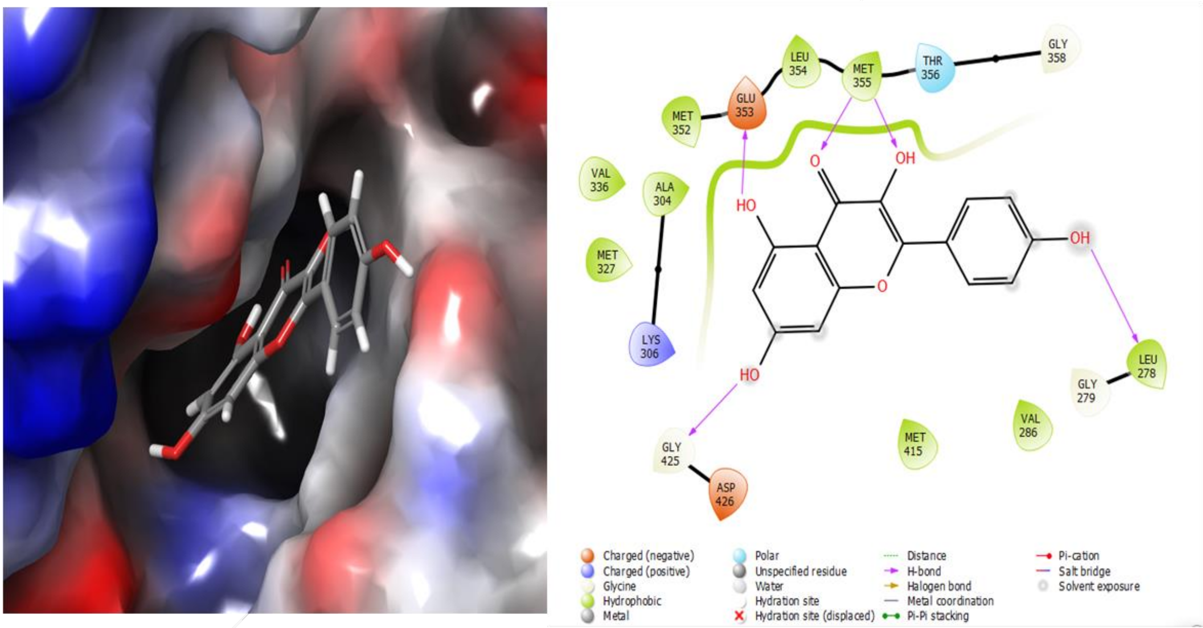
THR 356
MET 355
LEU 354
GLU 353
MET 352
MET 415
ALA 304
VAL 336
LYS 306
GLY 425
VAL 286
GLN 280
GLY 279
LEU 278
O
OH
HO
OH
OH
O
HO
Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Halogen bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge
Solvent exposure

(A)


LEU 354
MET 355
THR 356
GLY 358
GLU 353
MET 352
VAL 336
ALA 304
MET 327
LYS 306
O
OH
HO
OH
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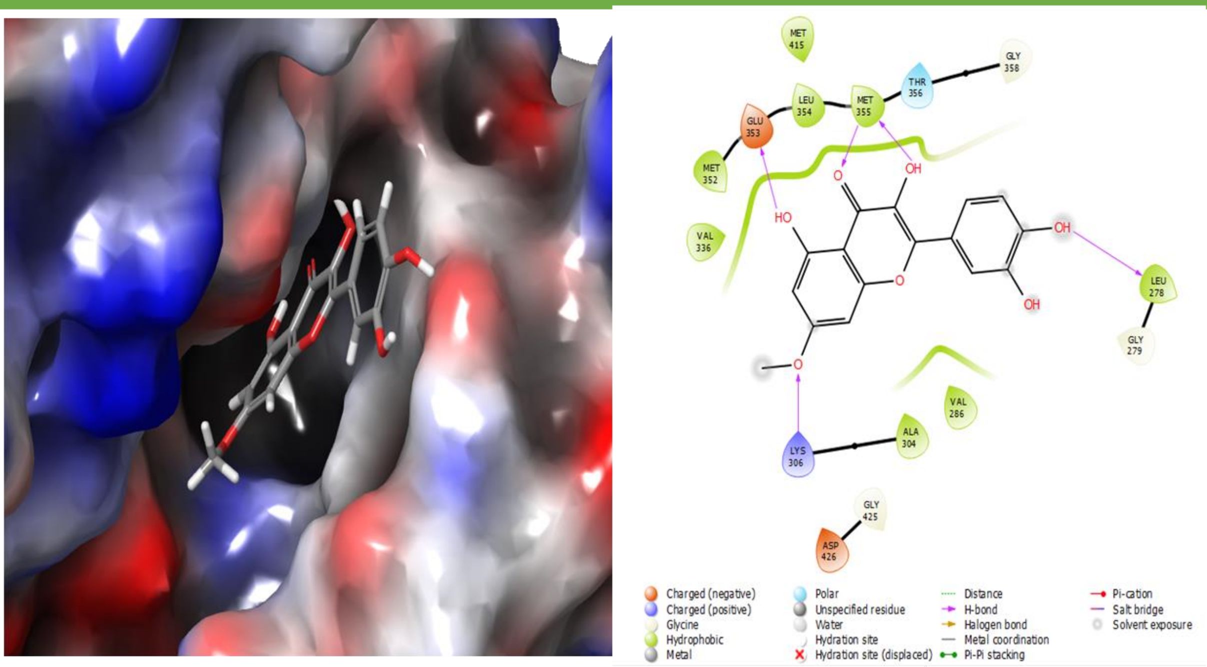
HO
GLY 425
ASP 426
MET 415
VAL 286
GLY 279
LEU 278
Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Halogen bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge
Solvent exposure

(B)



(C)

Figure 8: Intermolecular interactions of (A) quercetin, (B) kaempferol, and (C) rhamnetin with insulin-like growth factor-1-receptor

Table 4: Docking score and MM-GBSA post rigid docking

Name	**Para-hydroxy-benzoic acid (1)**	**Para-hydroxy-coumaric acid (2)**	**Caffeic acid (3)**	**Quercetin (4)**	**Kaempferol (5)**	**Rhamnetin (6)**	**Ferulic acid (7)**
Docking Score	-5.142	-4.922	-6.395	-8.425	-8.84	-9.385	-4.774
MMGBSA_ΔG_Bind	-16.3516	-21.5461	-24.6631	-42.811	-39.3028	-40.5971	-29.9584
MMGBSA_ΔG_Bind Coulomb	80.96294	87.9359	77.43172	-30.0433	-22.2266	-25.3496	75.19584
MMGBSA_ΔG_Bind Covalent	0.365253	0.707484	1.09186	5.586899	2.900419	6.324156	-3.07835
MMGBSA_ΔG_Bind HBond	-1.89688	-0.52778	-1.24349	-2.52237	-2.71795	-2.64201	-1.14783
MMGBSA_ΔG_Bind Lipo	-7.46844	-8.14198	-9.76507	-7.00138	-8.09104	-8.36927	-11.3458
MMGBSA_ΔG_Bind Solv_GB	-70.2267	-73.5759	-69.4857	21.62977	22.12441	22.91623	-66.81
MMGBSA_ΔG_Bind vdW	-18.0877	-27.9438	-22.6924	-30.4606	-31.2921	-33.4767	-22.7722

4. Discussion

There have been reports that some flavonoids can stop the growth of malignant cells [19,26]. Flavonoids are an important family of natural substances found in fruits, vegetables, and many plants. They are members of a group of secondary plant metabolites that have a polyphenolic structure. Their diverse metabolic and antioxidant characteristics have been associated with an array of medical conditions [27]. Research has demonstrated that Brachiaria grasses are rich in flavonoids [18]. According to Mohammed *et al*. [28], the concentration of flavonoids and phenolics may vary depending on how polar the extraction solvents are. This result is in line with our previous study [18] which concluded that Brachiaria grasses have an acceptable phenolic content. Studies show that the amount of phenol in a plant directly influences its antioxidant content. Phenolic compounds can decrease, donate hydrogen, and scavenge free radicals [29]. Brachiaria grasses contain substantial levels of phenolics, which may play a major role in their antioxidant properties.

Phytochemical screening was conducted utilising the High-Performance Liquid Chromatography (HPLC) method in order to examine the three grasses that were collected quantitatively. These findings showed that all three grasses have high concentrations of antioxidants such as phenolic acids and flavonoids. Compared to Brachiaria gayana and *Brachiaria sabia*, *Brachiaria marandu* has been found to have the greatest amount of bioactive chemicals by HPLC analysis. *Brachiaria marandu* thus contained a higher concentration of antioxidants. The results of this study are consistent with those of Boudalia et al. [30], who found that Brachiara grasses contain a variety of bioactive compounds that might enhance animal productivity.

Numerous investigations conducted over the past 20 years have indicated that this receptor plays a part in cell transformation, cancer cell growth, and metastatic processes [31,32]. Numerous studies have demonstrated a connection between this signalling system and the risk of getting cancer, even though no recurring cancer-specific mutations of the IGF-1R or its ligands have been identified to date [33,34]. The most frequent observations linked to IGF-1R overexpression or the formation of autocrine or paracrine signalling loops are related to dysregulated IGF signalling. Carcinogenic signalling loops are more prevalent and have been linked to a wide range of human cancers, whereas elevated expression levels of IGF-1R have been linked to colorectal and breast cancers. Paracrine signaling has mainly been described for breast cancer, where stromal cells have been shown to produce IGF-1 and IGF-2. Population studies have further highlighted the importance of IGF signaling in some of the most common cancers [35-38]. Elevated IGF-1 levels have been linked to an increased risk of cancer diagnosis, according to published evidence from epidemiological research [39,40]. Systematic evaluations of this data led to the inference that circulating IGF-1 levels are, in fact, associated with a risk of various common malignancies, even though the population studies did not always reach the same conclusions [41-43]. Prostate cancer, pre-menopausal breast cancer, and colorectal cancer were identified as having the strongest correlations between elevated levels of IGF-1 and the likelihood of receiving a cancer diagnosis [44-46]. Noteworthy, however, is that a major, comprehensive investigation identified no significant overall links between common germline variation in IGF1 and other genes implicated in IGF-1 metabolism and breast cancer [47-49].

IGF signalling and the IGF-1R have been implicated in human malignancies, according to a considerable body of research from mechanistic and epidemiological investigations. New therapeutic techniques that can be used with existing traditional therapy regimens have shown promise in targeting the IGF 1R. The findings indicate that seven different chemicals were consistently found in all three of the examined grasses: para-hydroxy-benzoic acid, para-hydroxy-coumaric acid, caffeic acid, quercetin, kaempferol, and ferulic acid. The molecule that is most prevalent and constant in the two grasses, quercetin (-40.5971), had the highest binding affinity to the insulin-like growth factor-1 receptor. This is seen by their relative extent of negative values, which indicate that, in comparison to other substances, they both require the least amount of energy to bind insulin-like growth factor-1 receptors. This work is consistent with that of Chen et al. [50] and Nagini *et al.* [51], which reported that flavonoids and phenolic acids exhibited a hydrophobic interaction with the intracellular structure of IGF-1 receptors.

5. Conclusion

Brachiaria marandu and sabia are excellent antioxidants. The existence of phenolic compounds has led to these results, which demonstrate strong antioxidant action. The most prevalent and reliable component in both grasses, quercetin, exhibited the highest binding affinity to insulin-like growth factor-1 receptors. Accordingly, this study shows that Quercetin, a constituent of Brachiaria grasses, binds to insulin-like growth factor-1 receptors (IGF-1R) which plays an important role in cancer cell proliferation. *In vivo* and *In vitro* research are also necessary to validate this in silico result.

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Conflict of Interest: Not applicable.

Ethical approval: Not applicable.

Informed consent: Not applicable.

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