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Phytochemical composition, antioxidant and cytotoxicity of the aqueous extracts of *Dracaena arborea* and *Bridelia ferruginea*: *in vitro* and *in silico* studies.

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Abstract

This study was undertaken to determine the phytochemical profile, antioxidant and cytotoxicity of the aqueous extracts of *Dracaena arborea* (DA) and *Bridelia ferruginea* (BF). The phytochemical composition, total phenolic (TP) and flavonoid (TF) contents of the extracts were determined by GC-MS, Folin Ciocalteu and $AlCl_3$ methods, respectively. The antioxidant power was estimated using DPPH and $ABTS^+$ radicals scavenging method, and cupric and ferric reducing capacity assay. The effect of extracts on hemolysis was also determined using red blood cells. Selected phytocompounds were docked against some oxidative stress (Keap1 and GST) and cytotoxicity (PARP10 and p90 RSK) proteins. The TP and TF content of BF was significantly ($p < 0.001$) higher than that of DA. The DPPH, $ABTS^+$, cupric and ferric reducing activity of BF were significantly ($p < 0.05 - 0.001$) higher than those of DA. DA decreased the viability of PC3, NIH3T3 and BT474 cells in a dose-dependent manner, while BF tended to feed the cells. Drug-Likeness and toxicity prediction of selected compounds found in the plant extracts were within the acceptable standards, according to Lipinski's rule. BF has the possibility to be exploited in the prevention/treatment of oxidative stress-related diseases, while DA could be a potential anticancer agent.

1. Introduction

In recent decades, the numerous health benefits of plant extracts have led to an exponential increase in phytotherapy research. Indeed, it has been reported that most phytocompounds are good for health as they possess a wide range of pharmacological activities such as antidiabetic, anticancer and antioxidant, among others [1–3]. *D. arborea*, known as *Keubgouh* in Bamileke (Cameroon) is a flowering tree in the Asparagaceae family [4]. This tall plant is native to West and Central Africa, and is used in many countries for the treatment of various diseases. In Cameroon, the roots of this plant are macerated in palm wine and used as sexual booster [4, 5]. In Benin, *D. arborea* is used by traditional healers for the treatment of dysentery, dysmenorrhea and malaria (stem barks), and skin infections (leaves), gonorrhea (roots) and hepatic dysfunctions (fruits) [6]. In Nigeria, the roots, leaves and fruits of *D. arborea* are used in the treatment of stomach ulcer, skin diseases and hypertension [7]. In Ghana, the decoction made with the mixture of *D. arborea* leaves, palm nut, *Nephrolepis biserrate* and *Dissotis multiflora* is used to prevent fatigue in woman during pregnancy and after childbirth [8]. We have previously reported that *D. arborea* improves sex hormones, fertility parameters and oxidative stress markers in varicocele rats [5, 9], and ameliorates sexual performances in diabetic rats [10]. Our research group also reported the effectiveness of *D. arborea* in improving the Leydig cell function of diabetic rats [11]. However, no previous studies have examined its chemical profile and antioxidant potential, and nor its cytotoxicity in cell lines.

B. ferruginea is a tropical tree (about 15 m high) in the family Euphorbiaceae. This plant is commonly called *Kisni* in Hausa (Ghana), *N'tchintchi* in Bassar (Togo), *Iroladan* or *Eepo ira* in Yoruba (Nigeria), *Tholinyi* in Susu (Sierra Leone), *Saguan* in Bambara (Mali), *Sagba* in Maninka (Guinea), *Dyimini* in Senufo (Cote d'Ivoire) and *Bemebenku* in Baatonun (Benin) [12–14]. In ethnomedicine, *B. ferruginea* is commonly used as an antidote against arrow poison, and for the treatment of various ailments, including diabetes, diarrhea, arthritis, dysentery and sexual dysfunctions [4, 14, 15]. Experimentally, *B. ferruginea* possesses

aphrodisiac [4], antidiabetic [16, 17], antidiarrheal [18] and anti-inflammatory [19] activities. However, the antioxidant and cytotoxicity of this plant have not been study. In the present study, the phytochemical screening (by GC-MS), and total phenolic and flavonoid contents of *D. arborea* and *D. arborea* were study. Furthermore, the antioxidant and cytotoxicity of the plant extracts were determined in PC3, NIH3T3 and BT474 cells. Finally, drug likeness and toxicity prediction, as well as molecular docking of selected compounds found in the plant extracts were investigated.

2. Materials and methods

2.1. Chemicals and reagents

N-butanol, ethyl alcohol, gallic acid, L (+)-ascorbic acid and acetic acid were procured from Daejung Co., Ltd. (Busan, ROK). Dimethyl sulfoxide (DMSO), trichloroacetic acid (TCA), aluminum chloride ($AlCl_3$), ferric chloride ($FeCl_3$), ferrous sulfate ($FeSO_4$), folin–Ciocalteu's phenol reagent, sodium carbonate (Na_2CO_3), potassium acetate (CH_3COOK), potassium persulphate ($K_2S_2O_3$), 2,2-diphenyl-1-picrylhydrazyl (DPPH), L neocuproine, ammonium acetate (NH_4CH_3COO), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), thiobarbituric acid (TBA), 2,2'-azo-bis(2-amidino propane dihydrochloride (ABAP) and thiazolyl blue tetrazolium bromide (MTT) were procured by Sigma-Aldrich (Yongin, ROK). Phosphate-buffered saline (PBS), fetal bovine serum (FBS) and penicillin–streptomycin (PS) solutions were obtained from Hyclone Laboratories (Logan, UT, USA). Dulbecco's Modified Eagle Medium (DMEM) and Ham's F-12 Nutrient Mixture medium were procured from ThermoFisher Scientific (Seoul, ROK). PC3, NIH3T3 and BT474 cells were obtained from the Korean Cell Line Bank (KCLB, Seoul, ROK).

2.2. Plant collections and preparation of aqueous extracts of *D. arborea* and *B. ferruginea*

D. arborea stem barks were harvested in Dschang (a city located in the West Region of Cameroon) and authenticated at the Cameroon National Herbarium (comparison with the specimen N° 25361/SFR/Cam). The stem barks were cut into small pieces, shade-dried for 12 days and transformed into powder. The aqueous extraction was performed by macerating 300g of powder in distilled water (2 L) for 72 hours. The solution was filtered through Whatman no.1 filter paper and the filtrate was oven dried at 55°C for 72 hours. 22 g of residue was obtained (extraction yield: 7.33% yield).

B. ferruginea stem barks were collected in Bangangté (town located at the West Region of Cameroon) and identified at the Cameroon National Herbarium (comparison with the specimen N° 42920/HNC). 300 g of *B. ferruginea* powder were macerated in distilled water (2 L) for 72 hours and filtered using Whatman no. 1 filter paper. 31 g of extract was obtained after evaporation of the filtrate (extraction yield of 10.33%).

2.3. Gas chromatography/mass spectrophotometry (GC-MS) analysis of *D. arborea* and *B. ferruginea*

The volatile compounds present in the aqueous extracts of *D. arborea* and *B. ferruginea* where identify by using a GC (Agilent 789A, Agilent, Santa Clara, CA, USA) / MS (Agilent 5975C; GC-MSD) system, according to the procedure described earlier [20, 21]. Briefly,1 µL of samples (at 1 mg/mL) was injected in a split mode (scan range of m/z 50–500) in the HP-5 capillary column at 250°C and helium (99.99%) gas was used as the carrier at a flow-rate of 1 mL/min. The total running time was 73 min. The compounds found in the plant extracts were identified by matching the GC-MS data of samples with the electronic library of W8N05ST.L.

2.4. Quantification of total phenolics (TP) and total flavonoids (TF)

The quantification of TP content in *D. arborea* and *B. ferruginea* extracts was carried out using the Folin Ciocalteu's method. Indeed, 100 µL of each extract (at 1 mg/mL) was added to Folin-Ciocalteu's phenol reagent (200 µL) and Na_2CO_3 (500 µL), and mixed well by gentle shaking. The mixture was incubated for 50 min at 25˚C and the absorbance was recorded at 760 nm. The TP content was quantified as milligram gallic acid equivalents per 100 g of dry weight (GAE/g DW).

The TF content of each extract was quantified as described earlier [22]. Briefly, 100 µL of each extract (at 1 mg/mL) was mixed with distilled water (250 µL) and ethanol (150 µL; 95%). Then, $AlCl_3$ (25 µL; 10%) and CH_3COOK (1M; 25 µL) were added and the solution incubated for 30 min at room temperature (25˚C). The absorbance was recorded at 415 nm and the TF content was estimated as milligram quercetin equivalent per gram of dry weight (mg QE/g DW).

2.5. DPPH and $ABTS^+$ free radical scavenging activity assay

The DPPH radical was estimated as described earlier [22]. Nine concentrations (7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000 µg/mL) of *D. arborea* and *B. ferruginea* and ascorbic acid were used. Briefly, 100 µl of each sample was added to the DPPH working solution (100 µL). After incubation in a dark at room temperature, the absorbance was recorded at 517 nm and the DPPH free radical scavenging percentage (%) was estimated [22].

The ABTS radical scavenging assay of extracts was estimated according to the literature [23]. Briefly, 100 µL of samples were mixed with 100 µL $ABTS^+$, incubated in the dark for 10 min and the absorbance was measured at 734 nm. The % of $ABTS^+$ radical was estimated using methanol and ascorbic acid as control solvent and standard, respectively.

2.6. Cupric (CUPRAC) and Ferric (FRAC) reducing antioxidant capacity assay

The CUPRAC assay was done as described in the literature [24]. Briefly, the mixture (100 µL of extracts + 61 µL $CuCl_2$ solution at 10 mM + 61 µL neocuproine at 7.5 mM + and 61 µL NH_4CH_3COO buffer at pH 7; 1.0 mM) was incubated in the dark for 60 min at 37˚C and the absorbance was recorded at 450 nm. The

CUPRAC of samples was estimated, using ethanol and ascorbic acid as control solvent and standard, respectively.

The FRAC of samples were determined based on previous studies [25, 26]. Briefly, the samples were mixed with $K_3[Fe(CN)_6]$ (500 µL, 30 mM) and PBS (175 µL, 0.6 M, pH 6.6), incubated for 20 min at 50°C, added to 500 µL of TCA (10%) and (1500 µL, 0.1%) and the absorbance was recorded at 700 nm. The FRAC of samples was estimated using ascorbic acid as standard [26].

2.7. Lipid peroxidation inhibition (LPI) assay

The estimation of LPI of samples was carried out using egg yolk homogenate as a lipid-rich media as described previously [27]. Briefly, 0.1 ml of samples was added to 0.5 ml of egg yolk homogenate (10%) and the mixture was adjusted to 1 ml with distilled water. $FeSO_4$ (0.07 M, 0.05 ml) was added, and the solution was incubated for 30 min. In addition, 1.5 ml of acetic acid (20%), 1.5 ml of TBA (0.8%) solution prepared SDS (1.1%), and 0.05 ml of TCA (20%) were added. The mixture was heated at 95°C for 60 min and n-butanol (5 ml) was added after cooling. The supernatant was collected after centrifugation (3000 rpm/10 min) and the absorbance was measured (at 532 nm). The LPI was then estimated [28].

2.8. Hemolysis assay

Homolysis experiment was done as described in our previous study [29]. Briefly, various concentrations (7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000 µg/mL) of plant extracts or controls (PBS and 1% Triton X-100) were mixed with 200 µL of red blood cells (RBCs) suspended in PBS and the mixture was incubated at 37°C for one hour. At the end of the incubation period, the absorbance of the supernatant was recorded at 540 nm and the hemolytic percentage was estimated [30].

2.9. Cell culture and cytotoxicity of D. arborea and B. ferruginea against PC3, NIH3T3 and BT474 cells

PC3, NIH3T3 and BT474 cells were obtained from the Korean Cell Line Bank (KCLB, Seoul, ROK) and cultured according to the suppliers' guidelines. The cytotoxicity of *D. arborea* and *B. ferruginea* extracts was determined by using 3-(4,5-di-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as described earlier [31]. Briefly, after seeding the cells in a 96-well plate and growing overnight, they were cultured for 24 hours with various concentrations (7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000 µg/mL) of plant extracts and the cell viability was determined. Indeed, 10 µL of MTT working solution (5 mg/mL) was added to each well and the plate was incubated in the dark for 3 hours. Then, the media was removed and 100 µL of DMSO was added to each well to solubilize formazan. The absorbance was measured at 570 nm and cell viability (%) was estimated. Furthermore, the DPPH, $ABTS^+$ and CUPRAC in all cell lines were measured as described in the previous sections.

2.10. *In silico* studies

2.10.1. Drug likeness and toxicity prediction

The drug-likeness and toxicity prediction of all the phytocompounds found in *D. arborea* and *B. ferruginea* were investigated following Lipinski's rule via SwissADME and as described earlier [32–34]. Molecular weight, number of hydrogen bonds (donor and acceptor), GI absorption, lipophilicity parameter, molar refractivity, and Lipinski violations were calculated using the SwissADME package. At the end of this test, compounds with high GI absorption satisfying all Lipinski's rules (5/5) were selected and used for molecular docking.

2.10.2. Molecular docking

The efficacy of phyto-compounds found in *D. arborea* and *B. ferruginea* against some antioxidant (Keap1 and GST) and cytotoxicity (PARP10 and p90 RSK) related proteins was evaluated as described in the literature [35]. Briefly, the proteins Keap1 (PDB ID: 2DYH), GST (PDB ID: code 5J41), p90 RSK (PDB ID: 4NUS), and PARP10 (PDB ID: 5LX6) were downloaded from the protein data bank (PDB; www.rcsb.org) and prepared for the study by removing water molecules and ligands, and adding polar hydrogen atoms. The active sites of proteins were built and saved as protein data bank (PDB) files. Veliparib [36] and LJH685 [37] were used as selective inhibitors of PARP10 and p90 RSK, respectively, while Nrf2 [38] and piperlongumine [39] were selected as Keap1 and GST inhibitors, respectively (Fig. 9). All ligands were prepared using UCSF chimera software (v1.16, San Francisco, CA, USA) and saved as Mol2 files. The proteins were later docked with the selected compounds from plant extracts (ligands) using ArgusLab (version 4.0.1). The results were visualized and analysed using the BIOVIA Discovery Studio Visualizer 2021 client.

2.11. Statistical analysis

The experiments were conducted in triplicate and the data are expressed as the mean plus or minus the standard error of the mean (SEM). Differences between the means were tested by ANOVA one-way followed by the post hoc Tukey HSD test using STATISTICA software, version 8.0 (StatSoft, Inc., Tulsa, USA). Significance level was set at 0.05 or less.

3. Results and discussion

3.1. GC-MS analysis and total phenolic (TP) and total flavonoid (TF) contents of D. arborea and B. ferruginea

The GC–MS spectrum of *D. arborea* and *B. ferruginea* confirmed the presence of various phytocomponents observed at a specific retention time (Fig. 1A, B). The GC–MS chromatograms of these compounds are shown in figures S1 and S2. There were 16 compounds identified from the GC–MS chromatogram of *D. arborea* and 32 compounds from *B. ferruginea* (Fig. 1A, S1 and Table S1, S2). Some of these compounds are known as antioxidant agents, according to the literature. For instance, AL-Adhreai et al [40] reported the antioxidant potential of isoxazolidine supported by *in vitro*, *in silico* and pharmacodynamic studies. In addition, N-propylacetamide found in *B. ferruginea* is used as an antiepileptic agent, but it anti-oxidant property is also reported [41]. No previous works on the GC-MS analysis of *D. arborea* have been found in the literature. The therapeutic potentials of these plants could

be attributed to their hight content in phenolics and flavonoids. As shown in table 3, the TP and TF contents in *B. ferruginea* were significantly ($p < 0.001$) greater than in *D. arborea.* There is no previous report on the quantification of TP and TF contents in *D. arborea* aqueous extract. In this study, the TP content in the aqueous extract of *B. ferruginea* was 295.25 ± 15.25 mg GAE/g DW, which is greater than the content reported by Afolabi et al. [42] (200.87 ± 1.51 mg GAE/g DW), and Mahomoodally et al. [43] (193.58 ± 0.98 and 187.84 ± 1.88 mg GAE/g DW in the methanolic and aqueous extracts of *B. ferruginea* stem bark, respectively). The TF content in *B. ferruginea* (10.42 ± 1.25 mg of QE/g DW) was comparatively lower than that reported by Mahomoodally et al. [43] (24.37–42.31 mg/g) in the aqueous leaf extract of *B. ferruginea*, but greater than that obtained by Afolabi et al. [42] (0.44 ± 0.01 mg QE/g DW) in the free phenolic extract of the aerial leaves of *B. ferruginea.* Moreover, Oladejo et al. [44] showed that n-hexane fraction of *B. ferruginae* contained greater total phenolic (14.14 ± 0.30 mg/GAE g) and flavonoid (7.82 ± 0.10 mg/QUE g) contents than ethyl acetate (13.42 ± 0.41 mg/GAE g; 5.76 ± 0.07 mg/QUE g), butanolic (8.42 ± 0.14 mg/GAE g; 2.60 ± 0.11 mg/QUE g) and residual aqueous fractions (6.57 ± 0.04 mg/GAE g; 3.78 ± 0.06 mg/QUE g). These variations in phenolic and flavonoid contents in *B. ferruginea* may be ascribed to factors such as climate, place, period of collection and extraction protocols [45, 46]. For instance, in the current work, the stem barks of *B. ferruginea* were harvested in May 2023 in the village of Bangangte in Cameroon and extracted my macerating in water, while Afolabi et al. [42] collected the aerial leaves of *B. ferruginea* in Nigeria (Ado-Ekiti, Ekiti State) and extracted using a free phenolic extraction method.

3.2. Effects of *D. arborea* and *B. ferruginea* on DPPH and $ABTS^+$ free radical scavenging activities

The DPPH assay evaluates the capacity of antioxidants to neutralize DPPH radicals through electron transfer reactions, while the $ABTS^+$ method measures the ability of an antioxidant compound to reduce the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) radical cation ($ABTS^{\bullet+}$) (dark blue color) into colorless ABTS [47]. There is no report on the $ABTS^+$ free radical scavenging activities of *D. arborea* and *B. ferruginea* in the literature. As shown in Fig. 2A and B, the DPPH and $ABTS^+$ free radical scavenging activities of *D. arborea*, *B. ferruginea* and ascorbic acids were dose-dependent (except DPPH activity of *D. arborea* at 2000 µg/ml). At all concentrations, we noticed that the activity of *B. ferruginea* was significantly ($p < 0.05 - 0.001$) higher than that of *D. arborea.* Moreover, *B. ferruginea* (2000 µg/ml) displayed the highest DPPH activity, compared to *D. arborea* and ascorbic acid. This strong antioxidant activity of *B. ferruginea* is consistent with the work of Olarewaju et al. [48] who showed that the DPPH free radical scavenging activity of *B. ferruginea* aqueous extract is higher than that of ethanolic and ethyl acetate extracts. Moreover, the beta-amyrin acetate fraction in *B. ferruginea* has been reported as a potent antioxidant agent due to its effective DPPH free radical scavenging potential [49]. In the current work, we observed that the DPPH free radical scavenging activity of *D. arborea* (7.8–2000 µg/ml) ranges from 20.99–47.50%. Similar, Nwaehujor et al. [50] showed that the methanolic extract of *D. arborea* (10–400 µg/ml) exhibits a moderate DPPH free radical scavenging activity (from 13% to 50,3%). The yellowish

colour observed at high concentration illustrate the ability of the plant extracts to reduce DPPH, probably by donating electron or hydrogen radical, as suggested earlier [50]. The intensity of the yellow color was more pronounce with *B. ferruginea*, which was correlated with its strong DPPH free radical scavenging activity at high concentrations (Fig. 2A).

3.3. Cupric and ferric reducing antioxidant power of *D. arborea* and *B. ferruginea*

The CUPRAC method gauges the electron transfer ability of sample components by assessing their reducing power [51]. On the other hand, the FRAC method test is based on the capacity of a compound to reduce a ferric salt (Fe^{3+}) to ferrous salt (Fe^{2+}) by electron transfer reaction [52]. These reliable methods were used in the present study to estimate the *in vitro* antioxidant potentials of *D. arborea* and *B. ferruginea.* For all compounds, a dose-dependent response was recorded. Indeed, at all concentrations, we noticed that the CUPRAC activity of *B. ferruginea* was higher than that of ascorbic acid and *D. arborea*, while ascorbic acid exhibited the strongest FRAC activity. The CUPRAC and FRAC activities of *B. ferruginea* were higher than that of *D. arborea* (Fig. 2CD). The low FRAC activity of *D. arborea* observed in this study corroborates previous reports which showed that the FRAC values of the methanolic extract of *D. arborea* at 400 µg/ml and 1000 µg/ml were 1.20 mM and 1.34 mM, respectively [50]. The potent FRAC activity of *B. ferruginea* has been discussed in previous reports. Indeed, Bothon et al. [53] reported that the FRAC activity of the ethanolic extract of *Bridelia ferruginea* (4.4 ± 0.06 µmol Fe II / g DW) is higher than that of *Ceiba pentandra* (0.14 ± 0.01 µmol Fe II / g DW). The FRAC activity of various fractions (n-hexane, n-butanol, ethyl acetate and residual aqueous fraction) of *B. ferruginea* has been previously published [44]. In addition, the powerful FRAC activity of free and bound phenolic-rich extracts of *B. ferruginea* has been reported [42]. The potent FRAC activity of *B. ferruginea* observed in the present study is due to its ability to reduce Fe^{3+} to Fe^{2+}.

3.4. Inhibition of lipid peroxidation by *D. arborea* and *B. ferruginea*

The ability of *D. arborea*, *B. ferruginea* and ascorbic acid to inhibit lipid peroxidation is shown in Fig. 3. The inhibitory activity of ascorbic acid was significantly ($p < 0.001$) higher than that of plant extracts. At low doses (7.8–62.5 µg/mL), *B. ferruginea* was more effective than *D. arborea*, while the inhibitory trend of both plants was similar at high doses. This result corroborates the work of Oloyede and Babalola [54] who illustrated the capacity of the ethanolic extract of *B. Ferruginea* to prevent oxidative stress by inhibiting lipid peroxidation. Moreover, the anti-lipid peroxidation effect of *B. ferruginea* aqueous extract has been reported [55]. The strong antioxidant potential of *B. ferruginea* could be due to its high phenolic and flavonoid contents, as suggested earlier [54].

3.5. Effects of *D. arborea* and *B. ferruginea* on hemolysis

Homolysis assay evaluates the effect of substance on erythrocyte membrane stability using RBCs. The effects of various concentrations (7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000 µg/mL) of plant

extracts on homolysis after incubation with human RBCs is presented in Fig. 4A, B. According to ASTM F756-00 norms, compounds with hemolysis percentages of more than 5%, between 5 and 2%, and less than 2% are classified as hemolytic, slightly hemolytic and non-hemolytic, respectively [56]. Thus, *D. arborea* was hemolytic at doses 2000 µg/mL (84.71 ± 8.93%), 1000 µg/mL (63.72 ± 10.20%) and 500 µg/mL (17.58 ± 4.34%), slightly hemolytic at dose 250 µg/mL (2.22 ± 0.46), and non-hemolytic at doses 125 to 7.8 µg/mL. Similarly, Okonkwo and Egeolu [57] reported that the ethanolic extract of *D. arborea* possesses no anti-hemolytic activity in the RBCs of Wistar albino rats pre-treated with Zidovudine. On the other hand, *B. ferruginea* was hemolitic at doses 2000 (13.70 ± 8.92%) and 1000 (5.31 ± 3.28%) and non-hemolytic at doses 500 to 7.8 µg/mL, which is consistent with the study of Karou et al. [58]. The hemolitic percentages of the two plant extracts were significantly ($p < 0.05 - 0.001$) lower than that of Triton X-100, used as a positive control. Overall, the hemolitic effect of *B. ferruginea* was lower than that of *D. arborea* (Figs. 4A, B). *B. ferruginea* (at moderate or low doses) did not cause any significant toxicity to RBC after incubation, probably meaning that it did not affect erythrocyte membrane stability *in vitro*.

3.6. Cytotoxicity of the aqueous extracts of D. arborea and B. ferruginea in PC3, NIH3T3 and BT474 cells

D. arborea decreased ($p < 01.05 - 0.001$) the viability of PC3, NIH3T3 and BT474 cells in a dose-dependent manner (Fig. 5A-C). At all doses, the cytotoxicity of *D. arborea* was most pronounced in BT474 cells. Indeed, the inhibitory values of BT474 cells after 24 hours of incubation with *D. arborea* at doses 2000, 1000 and 500 µg/ml were 5.56 ± 0.43%, 27.91 ± 2.2% and 29.47 ± 6.95%, respectively (Fig. 5C), indicating a potential candidate for anticancer drug development. The ability of *D. arborea* to decrease cell growth is in accordance with previous studies on the anticancer properties of this plant. Indeed, it has been proven that the methanolic extract of *D. arborea* exhibits an anticancer effect in human breast cancer cells (MDA-MB-231) by down-regulating VCAM-1 and EMT proteins through Akt/PKC pathway [59]. On the contrary, the aqueous extract of *B. ferruginea* had the tendency to feed the cells, since a dose-dependent increase in the viability of NIH3T3 and BT474 cells was observed after incubation (Fig. 5 BC). For instance, at doses 500, 1000 and 2000 µg/ml, the viability of NIH3T3 cells was 69.71 ± 5.1%, 69.88 ± 5.18% and 78.24 ± 10.62%, respectively. On the other hand, high BT474 cells viability was recorded after incubation with *B. ferruginea* at 500 µg/mL (98.40 ± 10.09%), 1000 µg/mL (98.55 ± 6.27%) and 2000 µg/mL (99.87 ± 4.67%). This trend of increase in the cell viability has been also reported with other plants like *Guibourtia tessmannii* [60], *Calophyllum Brasiliense* [61] and *Hunteria umbellata* [62], meaning that compounds found in the plant extracts could have the capacity to feed cells during incubation. However, the effects on *B. ferruginea* on cell viability may vary depending on the cells. In fact, the cells viability of PC3 cells after exposure to various concentrations of *B. ferruginea* was statistically unchanged ($P > 0.01$) (Fig. 5A). Similarly, Bothon et al. [63] showed that the ethanolic extract of *Bridelia ferruginea* has no cytotoxic activity on human fibroblast primary culture, as the percentage of cell survival being greater than 60% after exposure to various concentrations (0–25 µg/mL) of plant extract.

3.7. Antioxidant properties of *D. arborea* and *B. ferruginea* in PC3, NIH3T3 and BT474 cells

In the present study, PC3, NIH3T3 and BT474 cells were incubated with various concentrations of plant extracts and DPPH and ABTS radical scavenging activity, as well as ferric reducing power (FRP) were measured. In general, these oxidative stress parameters were increased (in a dose-dependent manner) in all cells after incubation with *D. arborea* and *B. ferruginea* extracts. In all cells, the DPPH (except in PC3 cells) and ABTS radical scavenging activity, and FRP of *B. ferruginea* were higher than that of *D. arborea* (Fig. 6A-I). Indeed, the NIH3T3 cells incubated with *B. ferruginea* (doses 250–1000 µg/mL), exhibited a significant ($P > 0.05$) increase in FRP, compared to the cells incubated with *D. arborea* (Fig. 6F). Moreover, the DPPH radical scavenging activity in PC3 cells after incubation with *B. ferruginea* (doses 250 µg/ml) was significant ($P > 0.05$) increased, compared to the cell exposed to *D. arborea* (Fig. 6G), which indicate the ability of these plants to act as free radical scavengers. The antioxidant activity of *B. ferruginea* observed in PC3, NIH3T3 and BT474 cells is consistent with the work of Oyebode et al. [63] who reported the free radical scavenging ability of *B. ferruginea in vitro*. Moreover, the DPPH scavenging activity of the aqueous and ethanolic extracts of *B. ferruginea* have been reported in FS5 fibroblasts cells [64], justifying the uses of this plant in the treatment of oxidative stress related diseases.

3.8. Drug likeness and toxicity prediction

Drug-Likeness and toxicity prediction of all compounds found in *D. arborea* and *B. ferruginea* are summarized in Tables S4 and S5. All compounds were within the acceptable standards, according to Lipinski's rule which states that a potential drug candidate should not violate no more that one of the following criteria: less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, a molecular mass below 500 daltons and less than 5 calculated octanol-water partition coefficient [65–67]. Compounds with high GI absorption satisfying all Lipinski's rules (5/5) were selected and used for molecular docking against Keap1, GST, PARP10 and p90 RSK enzymes (Figure S3).

3.9. Molecular docking results of selected compounds docked against Keap1 and GST

In the current study, the aqueous extracts of *D. arborea* and *B. ferruginea* exhibited a potent antioxidant activity, *B. ferruginea*, being the most effective. Hence, selected compounds found in these plants were docked against two antioxidant-related enzymes: Keap1 and GST. The importance of Keap1-Nrf2 pathway in the regulation of cellular oxidative stress is well documented. This pathway regulates various antioxidant markers such as heme oxygenase-1, peroxidase-1, superoxide dismutase and glutathione peroxidase [35, 68]. GST is one of the main antioxidant enzymes involved in the prevention of lipid peroxidation and maintenance of cellular homeostasis [69]. Our rationalization for selecting Keap1 and GST as oxidative stress markers and key targets of selected compounds from plant extracts is based on previous studies [35–37].

The binding affinity of selected compounds from *D. arborea* with Keap1 protein ranges from − 5.72 to -8.17 kcal/mol, which was below the value observed with Nrf2 (-11.82 kcal/mol). Among the compounds with good affinity with Keap1, we found that 2-deoxypentose displayed a strong interaction with the active pocket of Keap1 through three conventional hydrogen bonds with the amino acids Ile-559, Val-604

and Val-463 (Table S6, Fig. 7A). The docking of 1-butanamine, n-methyl or 1-propanamine, N,2-dimethyl with Keap1 indicated the binding interaction with the same amino acid (Ser-602) through two conventional hydrogen bonds, with the binding affinity of -5.90 and – 5.95 kcal/mol, respectively (Table S6, Fig. 7BC). Interestingly, 1,3-Propanediamine N-methyl displayed the best stability with Keap1 protein, compared to all compounds. Indeed, it was linked to Leu-557, Ala-510, Val-463 and Ile-416 residues of protein via six hydrogen bonds with a strong Van-der Walls interactions with nine amino acids, which could justify its strong stability (Table S6, Fig. 7D). Cis-cyclohexane-1,3-diamine showed a binding affinity of -6.73 kcal/mol and interacted with Keap1 through five conventional hydrogen bonds, while Nrf2 was linked to the protein via two hydrogen bonds (Table S6, Fig. 7E). The docking result of selected compounds from *B. ferruginea* against Keap1 is shown in table S6 and Fig. 8. In brief, the best stability with the protein was observed with 1,3-propanediamine, n-methyl (through 6 hydrogen bonds), followed by N-Methyl-1,3-propanediamine (via 5 hydrogen bonds) and ethen-1,2-diol (through 2 hydrogen bonds) (Table S7 and Fig. 8). However, Nrf2 (a Keap1 inhibitor) displayed the best binding affinity with Keap1.

Selected compounds from plant extracts were also docked against GST and piperlongumine (a GST inhibitor) was used for comparison. As expected, piperlongumine exhibited a strong stability with the binding pocket of GST through 3 conventional hydrogen bonds with Cys-101 and Tyr-108 residues (Table S6 and Fig. 7L). Docked interactions of selected compounds from *D. arborea* against GST are shown in table 9 and Fig. 7. The docking of 2-deoxypentose with GST had showed a binding affinity of -6.63 kcal/mol with a strong interaction through 2 hydrogen bonds (Cys-101 and Asp-306) (Fig. 7G). 2-deoxy-alpha-d-ribopyranose and 1,3-Propanediamine, N-methyl exhibited an affinity of -7.52 and – 5.98 kcal/mol, respectively, and interacted with the active pocket of GST via 2 hydrogen bonds (Table S9 and Fig. 7 HI). In addition, the strong Van-der Walls interactions and the presence of 3 carbon hydrogen bonds (Gln-259, Pro-261, Leu-260) between 2-deoxy-alpha-d-ribopyranose and GST may justify its high binding affinity. Cis-cyclohexane-1,3-diamine displayed good stability with GST compared to Piperlongumine, which could be due to the presence of 5 conventional hydrogen bonds between the ligand and Gln-135, Leu-132 and Ile-143 residues (Table S9 and Fig. 7 KL). Among the compounds found in *B. ferruginea*, 2-[(methylamino)methyl]cyclohexanol exhibited the highest binding affinity (-8.66 kcal/mol) with GST, which was similar to that of Piperlongumine (-8.85 kcal/mol), used as GST inhibitor in this study (Table S7). Overall, other ligands displayed similar binding affinity with the protein, but their stability was quite different. For instance, 2-[(methylamino)methyl]cyclohexanol was linked to the active pocked of GST via one conventional hydrogen bond (Arg-282), while N-propylacetamide (Arg-221 and Asn-412) and N-Methyl-1,3-propanediamine (Ile-203 and Asn-204) were attached to the protein through two conventional hydrogen bonds (Table S7 and Fig. 8 GHI). In addition to three hydrogen bonds with the residues Cys-101 and Tyr-108 of GST, the highest binding affinity of piperlongumine could be due to the high Van-der Walls interactions with 11 amino acids of the active site of GST (Table S7 and Fig. 8L).

Based on these results, it appears that compounds identified in *D. arborea* and *B. ferruginea* have a unique capacity to bind to the active pocket of Keap1and directly inhibit the crucial Keap1–Nrf2 interaction, leading to free Nrf2 release. Moreover, the strong binding affinity of these compounds with GST indicates their antioxidant potential *in silico*, which corroborates the *in vitro* antioxidant activity of

these plants observed in this study. These findings are consistent with other reports on these plants using animal models. For instance, *D. arborea* has the ability to boost the antioxidant markers in rats with varicocele [9]. *B. ferruginea* exhibits a potent antioxidant potential in N-nitrosodiethylamine-treated rats by improving ROS detoxification [70].

3.10. Molecular docking results of selected compounds docked against PARP10 and p90 RSK

PARP10 is involved in various aspects of cell function and its activity is associated to cell survival [71] and DNA repairing [72]. p90 RSK is a member of RSK family involved in the regulation of various cellular and metabolic processes, including cell growth [73, 74], cell signaling [75], cellular homeostasis [76] and DNA repair [77]. To predict the cytotoxicity of selected compounds from *D. arborea* and *B. ferruginea*, molecular docking on PARP10 and p90 RSK proteins was performed. Veliparib [36] and LJH685 [37] were used as a selective inhibitor of PARP10 and p90 RSK, respectively, according to previous reports.

The binding affinity of selected compounds from *D. arborea* against PARP10 was similar, but they were matched differently at the active pocket of the protein. Docked interactions of 2,3-butanediol with PARP10 had shown the interactions with Gly-1077 and His-1076 through 3 hydrogen bonds in addition to a strong Van-der Walls interactions with five amino acids (Table S8 and Fig. 9A). 2-deoxypentose interacted with the active site of PARP10 via 4 conventional hydrogen bonds with Arg-1146, Arg-1147, Gly-1145 and Val-1102, but they were only one Van-der Walls interaction with Tyr-1103 and no Alkyl/Pi-Alkyl interactions (Table S8 and Fig. 9B). Among all compounds, the best stable ligand was 2-deoxy-alpha-d-ribopyranose, as it was well-matched in the PARP10 pocket through five hydrogen bonds with Ala-962, Arg-957, Gly-959 and Arg-961, which can also justify its strong binding affinity (Table S8 and Fig. 9C). 1,3-Propanediamine, N-methyl had three hydrogen bonds with the protein via Tyr-1075 and Tyr-1108 residues, while Cis-cyclohexane-1,3-diamine was linked to PARP10 by two conventional hydrogen bonds (Tyr-1108, Tyr-1075) (Table S8 and Fig. 9DE). Veliparib used as control in this experiment exhibited the highest binding affinity (-8.26 kcal/mol) with PARP10, but was not well matched like 2-deoxy-alpha-d-ribopyranose. Thus, its high binding affinity with the protein could be due to the strong Van-der Walls interaction with 10 amino acids (Thr-1079, Asp-1085, Phe-1091, Glu-1106, Arg-1093, Val-1107, Asn-1099, Tyr-1108, His-1076, Thr-1078) as shown in Table S8 and Fig. 9F. Among the compounds isolated from *B. ferruginea*, we found that *2*-[(methylamino)methyl]cyclohexanol exhibited the best binding affinity with PARP10 (-9.80 kcal/mol), which was higher than that of Veliparib (-8.26 kcal/mol) (Table S9). Isobutyramide and N-Methyl-1,3-propanediamine interacted with the active site of PARP10 via 3 conventional hydrogen bonds, while 2-[(methylamino)methyl]cyclohexanol, heptylamine and 4-octen-3-one were attached to the protein through 2 hydrogen bonds (Table S9; Fig. 10A-E). The hydrogen on the pyridine nitrogen of PARP10 formed a conventional hydrogen bond with Asn-1092, while 2 hydrogens of the pyrimidine nitrogen formed 2 hydrogen bonds with the amino acids Cys-1096 and Phe-1095 (Fig. 10F). As reported in previous reports, the main amino acids of the active pocket of PARP10 that interact with compatible ligands are amino acids Tyr-914, Tyr-919, Tyr-932, Ala-911, Ala-921, Gly-888, Ser-927, His-887, Leu-926 and Asn-910 [36, 78, 79]. In the current work, we found that the majority of

compounds found in the plant extracts were bound to the active sites of PARP10 via these amino acids. For instance, cyclopropanecarboxamide was linked to Ser-927 via one hydrogen bond (Table S8), while 2-[(methylamino)methyl]cyclohexanol was bound to Tyr-919 through 2 hydrogen bonds (Table S9). Cyclopropanecarboxamide and 4-octen-3-one were linked to two amino acids: (Ser-927; Tyr-919) and (Ala-921, Ser-927), respectively, via two hydrogen bonds (Table S9).

LJH685 used as a selective p90 RSK inhibitor had the best binding affinity (-9.61 kcal/mol) with the protein, but was not well-fitted into the RSK pocket, compared to other ligands from plant extracts (Table S8). For instance, 2-deoxypentose, 2-deoxy-alpha-d-ribopyranose and 1,3-Propanediamine, N-methyl- formed 3 hydrogen bonds with p90 RSK, while LJH685 interacted with the protein only through one conventional hydrogen bond (Table S8; Fig. 9H-J). Cyclopropanecarboxamide possessed a binding energy of -6.96 kcal/mol and interacted with the active site of p90 RSK via one hydrogen bond (with Lys-142), but exhibited the highest Alkyl/Pi-Alkyl interactions (Leu-70, Met-99, Val-101, Phe-83) among all ligands found in *D. arborea* (Table S8; Fig. 10).

The docking of compounds found in *B. ferruginea* showed that 2-[(methylamino)methyl]cyclohexanol displayed the highest binding affinity with p90 RSK (-10.60 kcal/mol) and was well-matched to the active pocket via 3 conventional hydrogen bonds with amino acids Leu-285, Ala-283 and Arg-300 (Table S9; Fig. 10H). The additional Alkyl/Pi-Alkyl interactions (with 2 amino acids: Met-287 and Arg-305) and Van-der Walls interactions (with 6 amino acids: Leu-299, Lys-284, Ile-280, Phe-268, Pro-237 and Lys-304) may justify its high binding affinity with p90 RSK. N-Methyl-1,3-propanediamine and 1,3-propanediamine, n-methyl- also possessed 3 hydrogen bonds with p90 RSK, but displayed lower binding affinity (-5.64 kcal/mol and − 5.64 kcal/mol, respectively) (Table S9; Fig. 10IJ). The docking of 4-methoxy-2-butyn-1-ol and 4-octen-3-one with p90 RSK had shown interaction with one amino acid through one hydrogen bond, with the binding energies of -6.45 kcal/mol and − 8.07 kcal/mol, respectively. However, 4-octen-3-one displayed additional Alkyl/Pi-Alkyl interactions with seven amino acids (Val-82, Lys-100, Ala-98, Leu-147, Val-131, Leu-150, Leu-200) which could justify its high binding affinity (Table S9; Fig. 10JK).

In the present study, we found that *B. ferruginea* exhibited a potent antioxidant activity, while *D. arborea* decreased the proliferation of PC3, NIH3T3 and BT474 cells. The proposed mechanism of action of these plants is summarized in Fig. 11. Based on the results obtained, it could be proposed that *B. ferruginea* could exhibit its potent antioxidant activity by inhibiting the peroxidation of cellular lipids (i), which could promote fatty acid oxidation at the level of mitochondria (ii), resulting in the reduction of ROS and finally leading to the reduction of oxidative stress (iii). In addition, this plant could directly increase the production of antioxidant enzyme [63, 64] and Keap1(iv), as also reported by previous authors. The good binding interactions of selected compounds against Keap1 and GST supports this probable mechanism. Bax, cytochrome C and caspases 3/9 are the main proapoptotic factors involved in the intrinsic pathway of apoptosis. *D. arborea* could activate Bax (i), which could enter mitochondria and induce release of mitochondrial cytochrome C (ii). This proapoptotic factor could then activate caspase 3 and 9 (iii), which could promote apoptosis and decrease cell proliferation. Under stress or pathological conditions, the activation of ERK1/2 induces apoptosis and cell death via p90 RSK and other various signalling

cascades [80]. In the current study, the phytocompounds found in *D. arborea* exhibited a strong interaction with the active pocket of p90 RSK. For instance, 2-deoxy-alpha-d-ribopyranose was the most stable compounds, as it was attached to the active pocket of the protein via 5 conventional hydrogen bonds. This ligand could activate ERK1/2 and phosphorylate p90 RSK (iv), which in turn could increase apoptosis and decrease cell proliferation. Another partway could be via PARP10 phosphorylation. It is well known that PARP10 modulates apoptosis, DNA repair and cell viability [81–83]. This ligand could directly modulate PARP10 phosphorylation (v), which may promote apoptosis and decrease cell proliferation. Further mechanistic studies are highly needed.

4. Conclusion

The total phenolic and flavonoid contents of *B. ferruginea* were higher than that of *D. arborea*. *B. ferruginea* exhibited a potent antioxidant potential, while *D. arborea* decreased the viability of PC3, NIH3T3 and BT474 cells after incubation. The hemolysis study showed no potential toxicity of low or moderate doses of *D. arborea* (7.8 to 250, µg/mL) and all doses of *B. ferruginea.* Drug-Likeness and toxicity prediction of selected compounds found in both extracts were within the acceptable standards, according to Lipinski's rule. Selected compounds from the plant extracts exhibited a strong binding affinity with Keap1, GST, PARP10 and p90 RSK, which support the *in vitro* results. *B. ferruginea* has the possibility to be exploited in the prevention and treatment of oxidative stress-related diseases, while *D. arborea* could be a potential anticancer agent. These findings could justify the ethnomedicinal uses of *D. arborea* and *B. ferruginea*.

Abbreviations

ABAP: 2,2'-azo-bis(2-amidino propane dihydrochloride, ABTS: (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), AChE: acetylcholinesterase, $AlCl_3$: aluminum chloride, CH_3COOK: potassium acetate, CUPRAC: cupric reducing antioxidant capacity, DMEM: Dulbecco's Modified Eagle Medium, DMSO: Dimethyl sulfoxide, Keap1: Kelch-like ECH-associated protein 1, PARP10: poly(ADP-ribose) polymerase family member 10, p90 RSK: p90 ribosomal S6 kinases, PDB: protein data bank, DPPH: 2,2-diphenyl-1-picrylhydrazyl, FBS: fetal bovine serum, $FeCl_3$: ferric chloride, $FeSO_4$: ferrous sulfate, GST: glutathione S-transferase, FRAC: Ferric reducing capacity, H_2O_2: hydrogen peroxide, TP: total phenolic, TF total flavonoid, GC-MS: Gas chromatography-mass spectrometry, RBCs: red blood cells, $K_2S_2O_3$: potassium persulphate, MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Na_2CO_3: folin–Ciocalteu's phenol reagent, sodium carbonate, Na_2CO_3: sodium carbonate, NH_4CH_3COO: ammonium acetate, ROS: Reactive Oxygen Species, PBS: Phosphate-buffered saline, PS: penicillin–streptomycin, SDS: Sodium dodecyl sulfate, TBARS: thiobarbituric acid reactive substances, TCA: trichloroacetic acid, TBA: thiobarbituric acid.

Declarations

CRediT authorship contribution statement

Patrick Brice Defo Deeh carried out the research work and drafting the initial version of the manuscript. **Moonhae Kim, Anbazhagan Sathiyaseelan** and **Kumar Vishven Naveen** participated in phytochemical analysis and molecular docking experiment and manuscript drafting. **Myeong-Hyeon Wang** supervised the study and approved the final draft of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this paper.

Data availability statement

All data and materials are available upon request.

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Figures

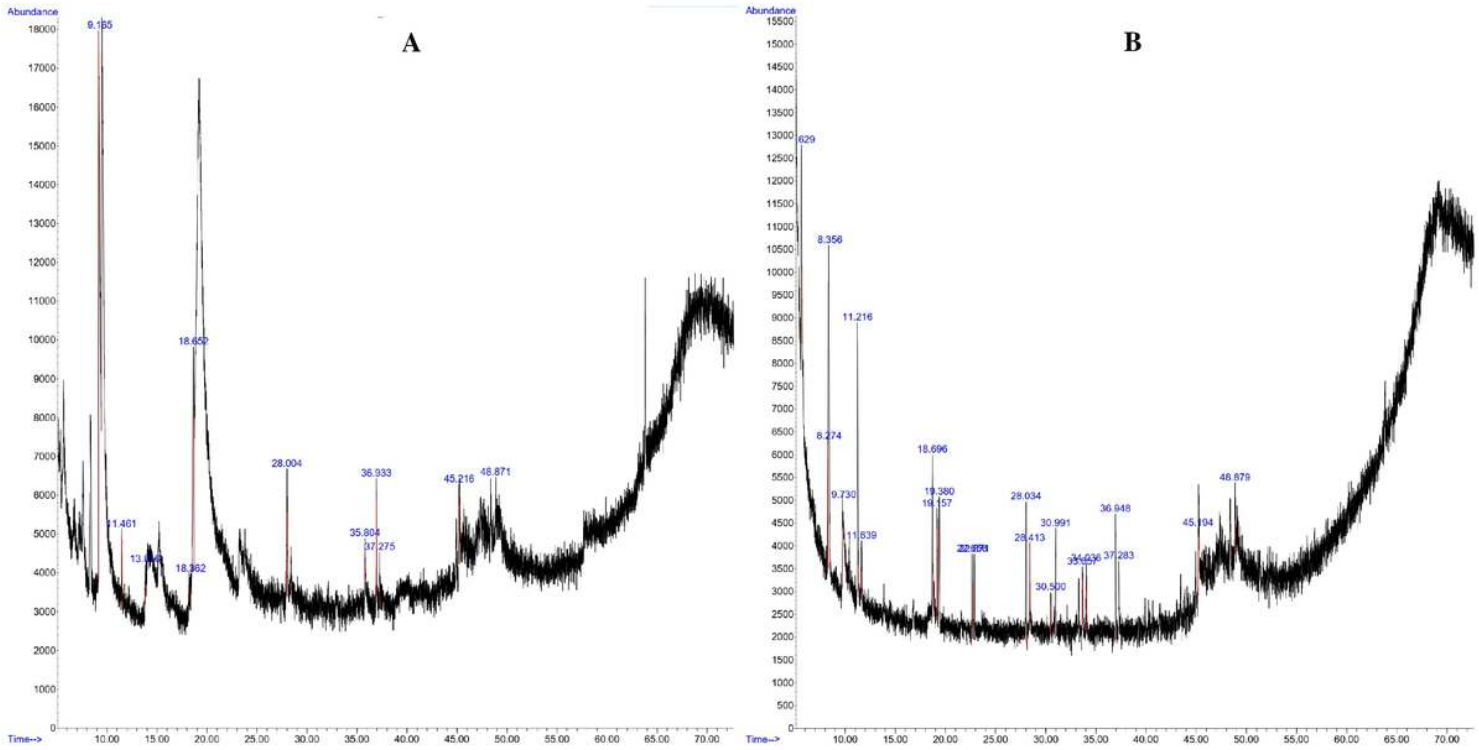

Figure 1

The major phytocompounds detected in the aqueous extracts of *D. arborea* (A) and *B. ferruginea* (B) using GC-MS analysis.

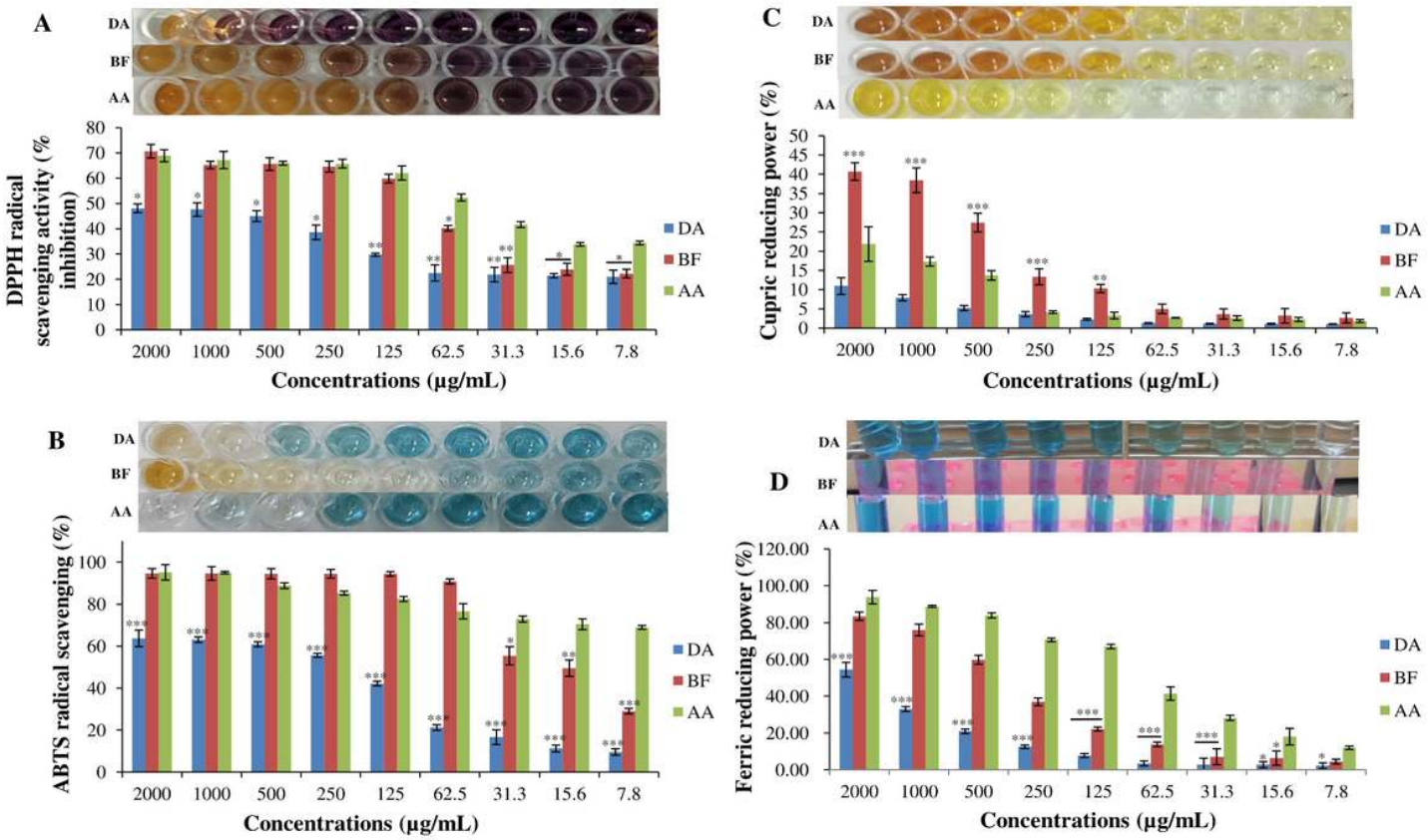

Figure 2

DPPH (A) and ABTS (B) radical scavenging activity, and cupric (C) and ferric (D) reducing power of *D. arborea* and *B. ferruginea*. DA: *Dracaena arborea;* BF:*Bridelia ferruginea;* AA: ascorbic acid. Number of replicate = 3. Data represent mean ± standard error of the mean (SEM). A concentration-dependent antioxidant potential of DA, BF and AA was recorded. For all parameters, the activity of BF was higher than that of DA. *p<0.05; **p<0.01; ***p<0.001: compared to AA.

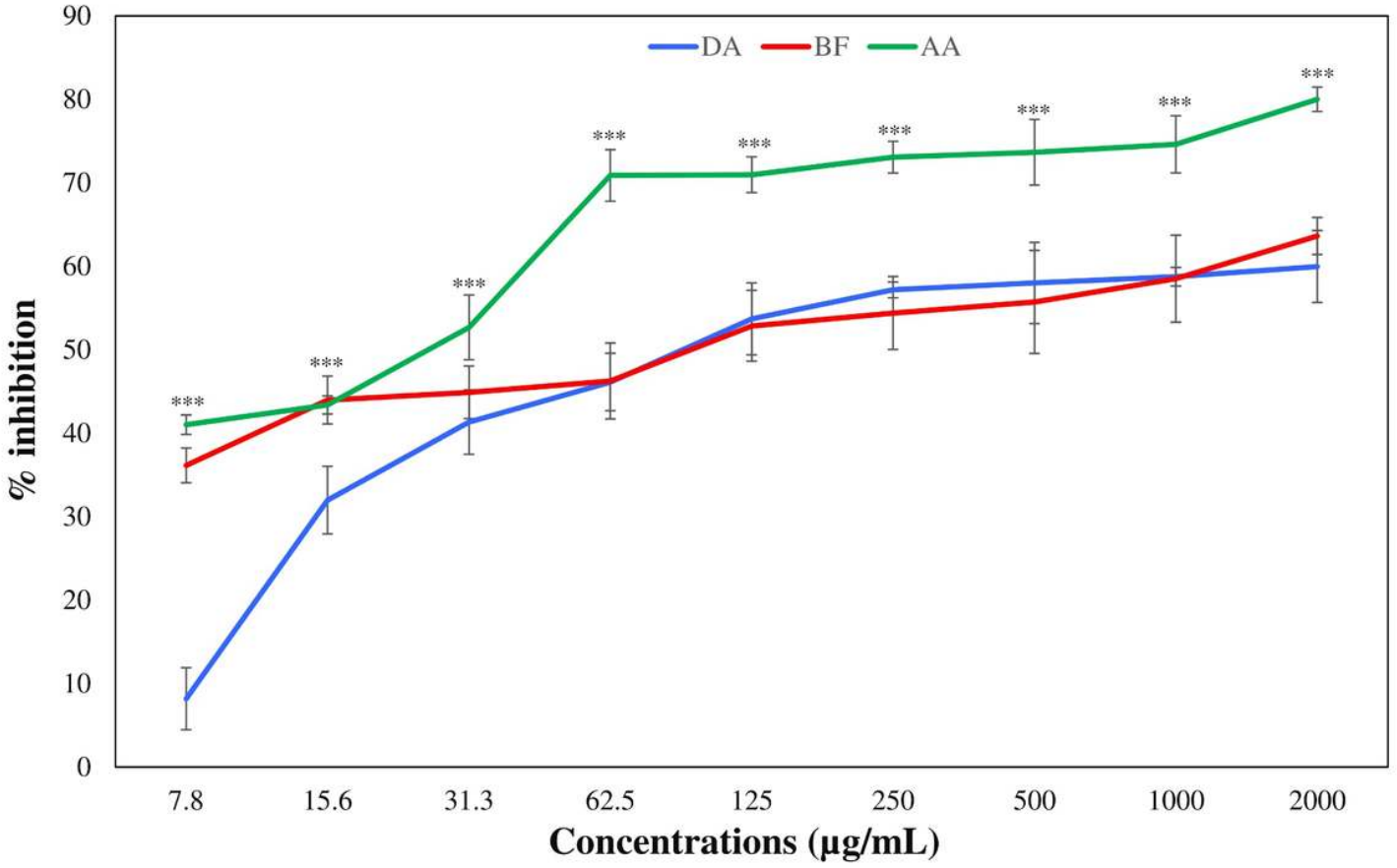

Figure 3

Effects of *D. arborea* (DA), *B. ferruginea* (BF) and ascorbic acid(AA) onlipid peroxidation inhibition. Number of replicate = 3. ***p<0.001: compared with DA. Data represent mean ± standard error of the mean (SEM). Egg yolk homogenate was used a lipid-rich media and the ability of plant extracts to inhibit lipid peroxidation was evaluated using TBA reactive substances (TBARS) assay. All compounds inhibited lipid peroxidation in a dose-dependent manner.

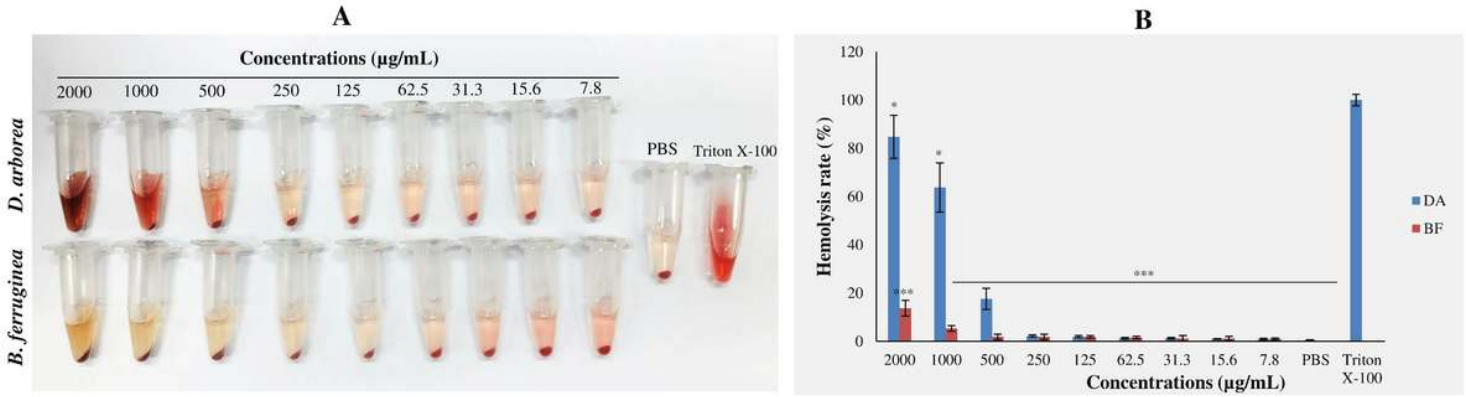

Figure 4

Hemolytic activities of *D. arborea* and *B. ferruginea.* (A)Photographs of hemolysis of RBCs after incubation with the plant extracts. **(B)**Percentage of hemolysis of RBCs after treatments. The cells were incubated with various concentrations (7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000 µg/ml) of plant extracts and the hemolytic activity was determined as described in the material and methods. PBS and Triton X-100 were used as negative and positive controls, respectively. Data represent mean ± standard error of the mean (SEM). Experiments were performed in triplicate. *p<0.05; ***p<0.001: compared to TritonX-100. A concentration-dependent activity was recorded.

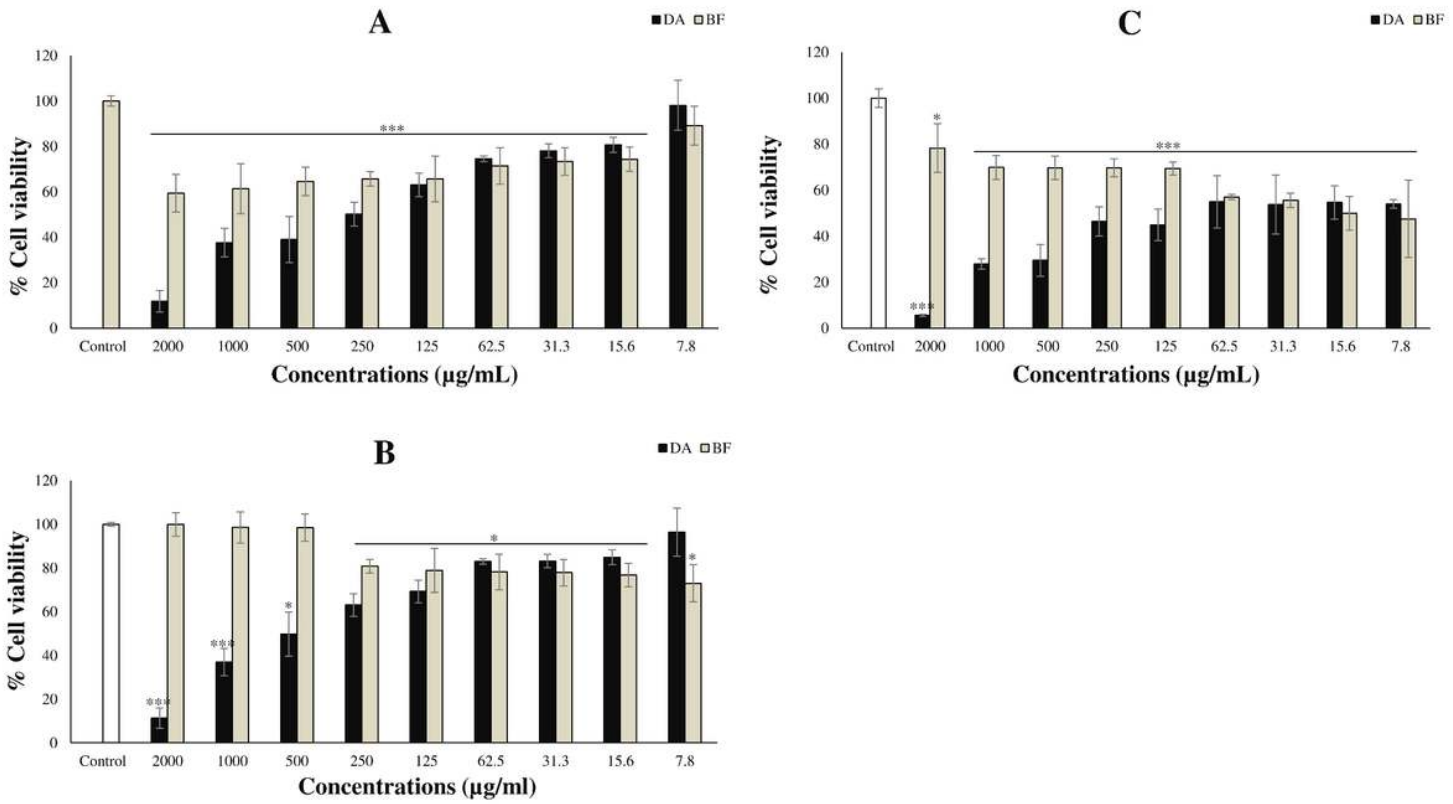

Figure 5

Cells viability of PC3 (A), NIH3T3 (B) and BT474 cells (C) after incubation with various concentrations of *D. arborea* and *B. ferruginea*. The cells were incubated for 24 hours with various concentrations (7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000 µg/ml) of DA and BF, and cell viability was determined by MTT. *DA: Dracaena arborea;* BF:*Bridelia ferruginea.* The effect of the two plant extracts on the viability of PC3, NIH3T3 and BT474 cells was dose-dependent. DA decreased the viability of all cells, while BF tended to feed the cells.Experiments were performed in triplicate. Each bar represents the mean ± SEM. *p<0.05; ***p<0.001: compared to control.

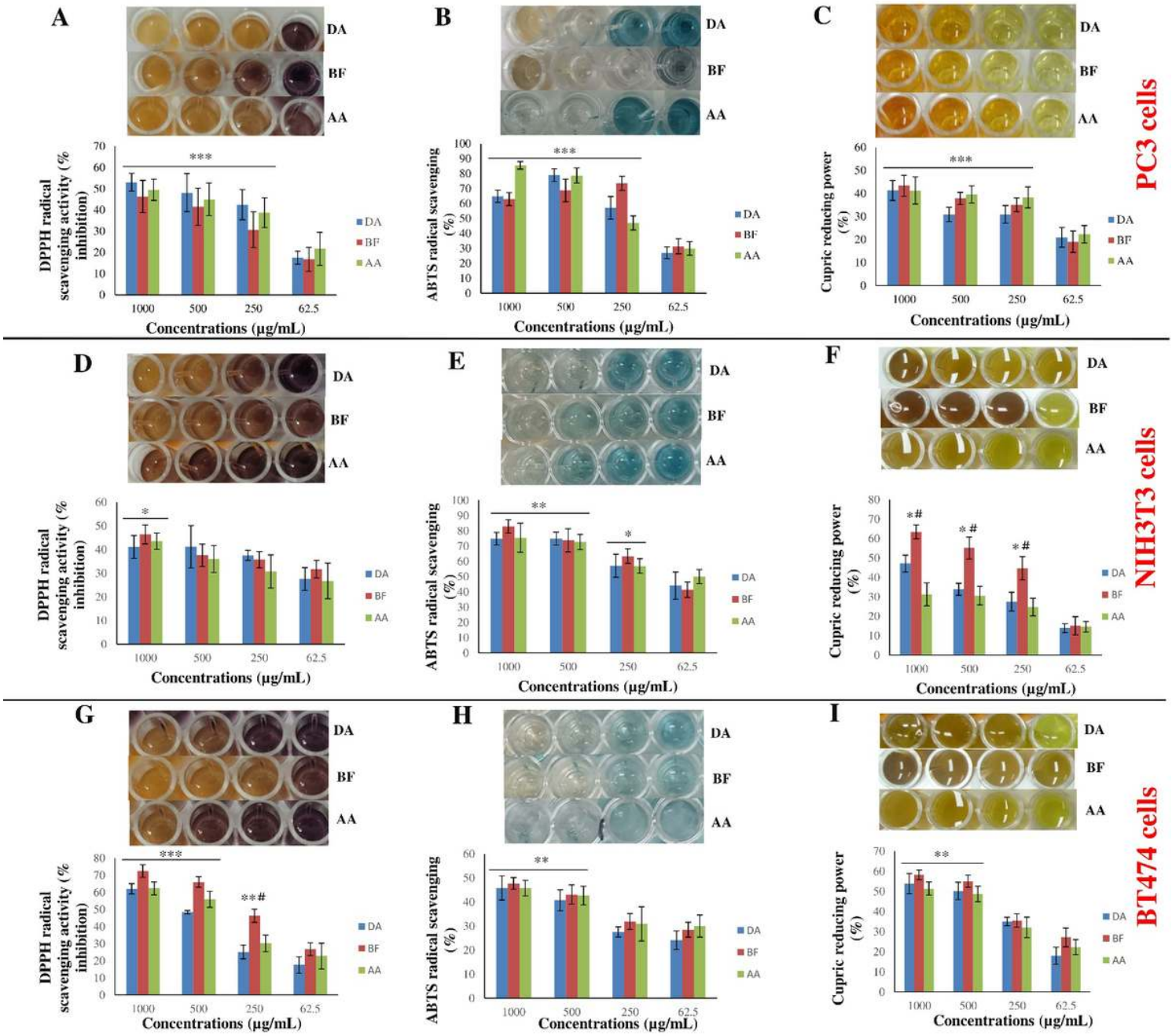

Figure 6

Effects of *D. arborea* and *B. ferruginea*on DPPH and ABTS radical scavenging activity, and ferric reducing power in PC3 (A-C), NIH3T3(D-F) and BT474 cells (G-I). DA: *Dracaena arborea;* BF: *Bridelia ferruginea;* AA: ascorbic acid. Number of replicate = 3. *p<0.005; **p<0.01; ***p<0.001: compared with dose 7.8 µg/ml. #p<0.05: compared with AA same dose. Data represent mean ± standard error of the mean (SEM).

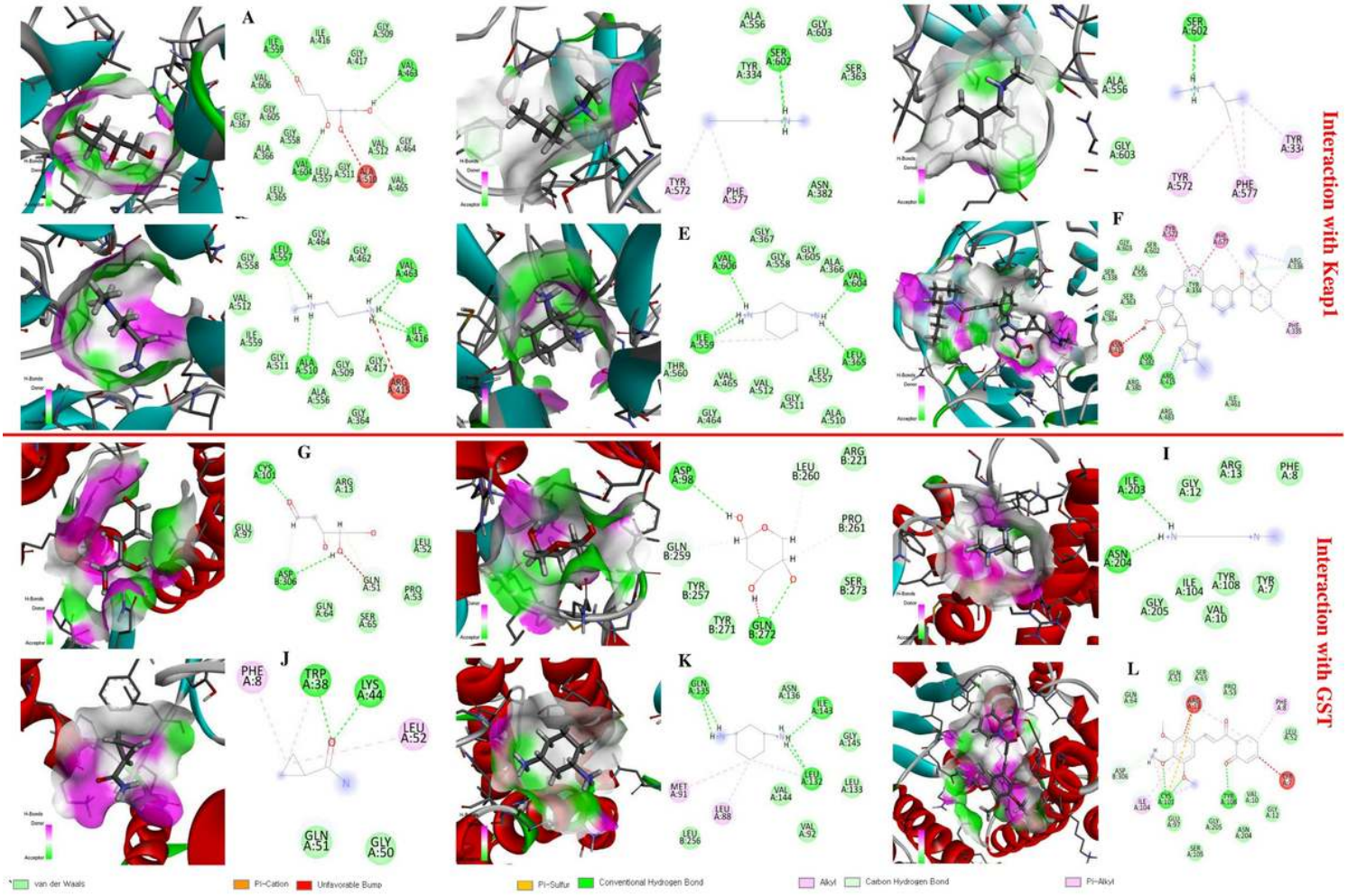

Figure 7

3D and 2D representations of the molecular interactions of selected compounds found in *D. arborea* interacting with Keap1 **(A-F)** and glutathione S-transferase **(G-L). (A)**2-deoxypentose, **(B)** 1-butanamine, n-methyl-, **(C)**1-Propanamine, N,2-dimethyl-, **(D)**1,3-Propanediamine, N-methyl-, **(E)**Cis-cyclohexane-1,3-diamine, **(F)** Nrf2. **(G)** 2-deoxypentose, **(H)**2-deoxy-alpha-d-ribopyranose, **(I)** 1,3-Propanediamine, N-methyl-, **(J)**Cyclopropanecarboxamide, **(K)** Cis-cyclohexane-1,3-diamine, **(L)**Piperlongumine.

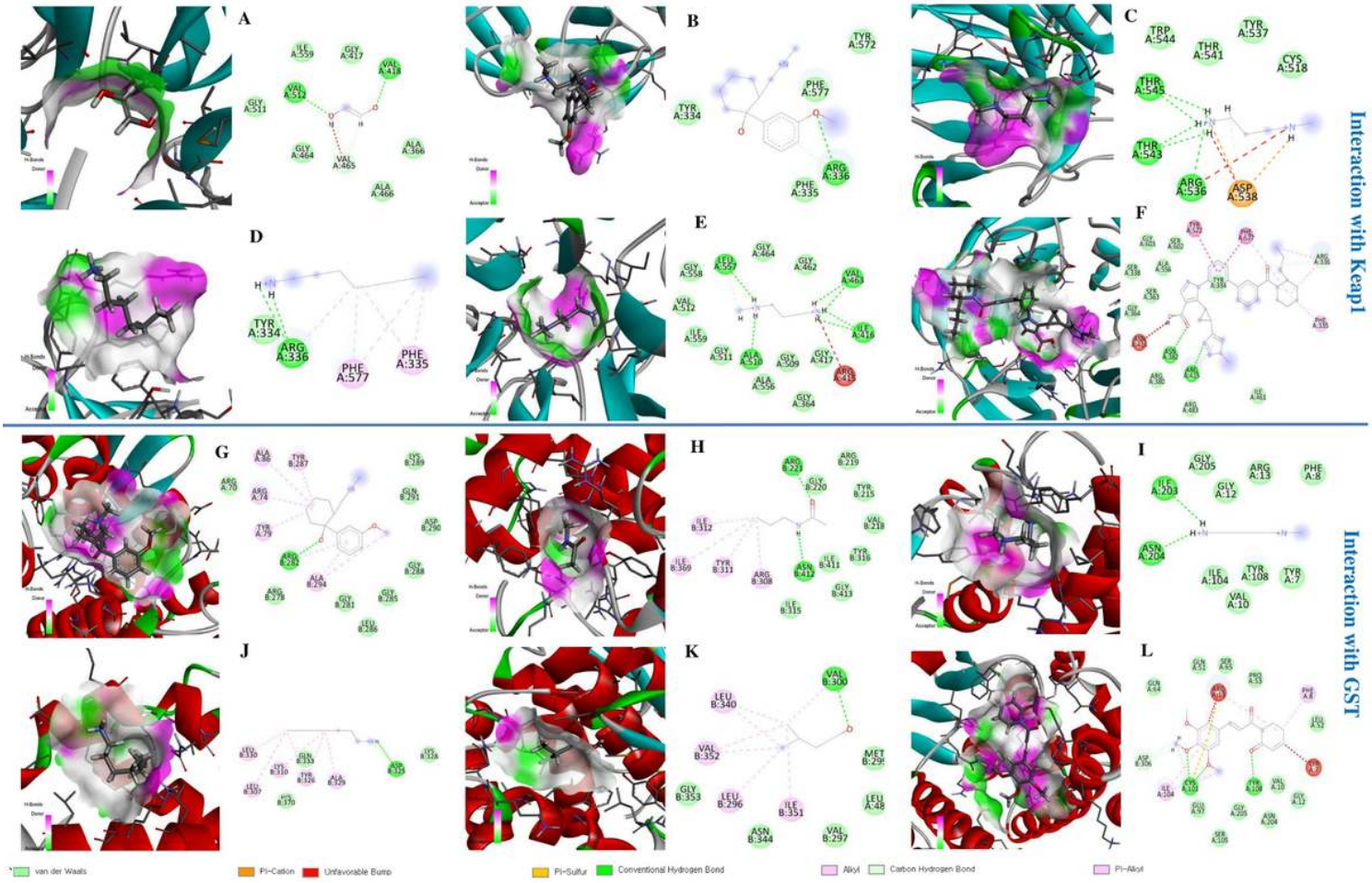

Figure 8

3D and 2D representations of the molecular interactions of selected compounds identified from the aqueous extract of *B. ferruginea* interacting with Keap1 **(A-F)** and glutathione S-transferase **(G-L). (A)** ethen-1,2-diol, **(B)**2-[(methylamino)methyl]cyclohexanol, **(C)** N-Methyl-1,3-propanediamine, **(D)**heptylamine, **(E)** 1,3-propanediamine, n-methyl-, **(F)** Nrf2, **(G)**2-[(methylamino)methyl]cyclohexanol, **(H)** N-propylacetamide, **(I)**N-Methyl-1,3-propanediamine, **(J)** heptylamine, **(K)** 1-butanol, 3-methyl-, **(L)** Piperlongumine.

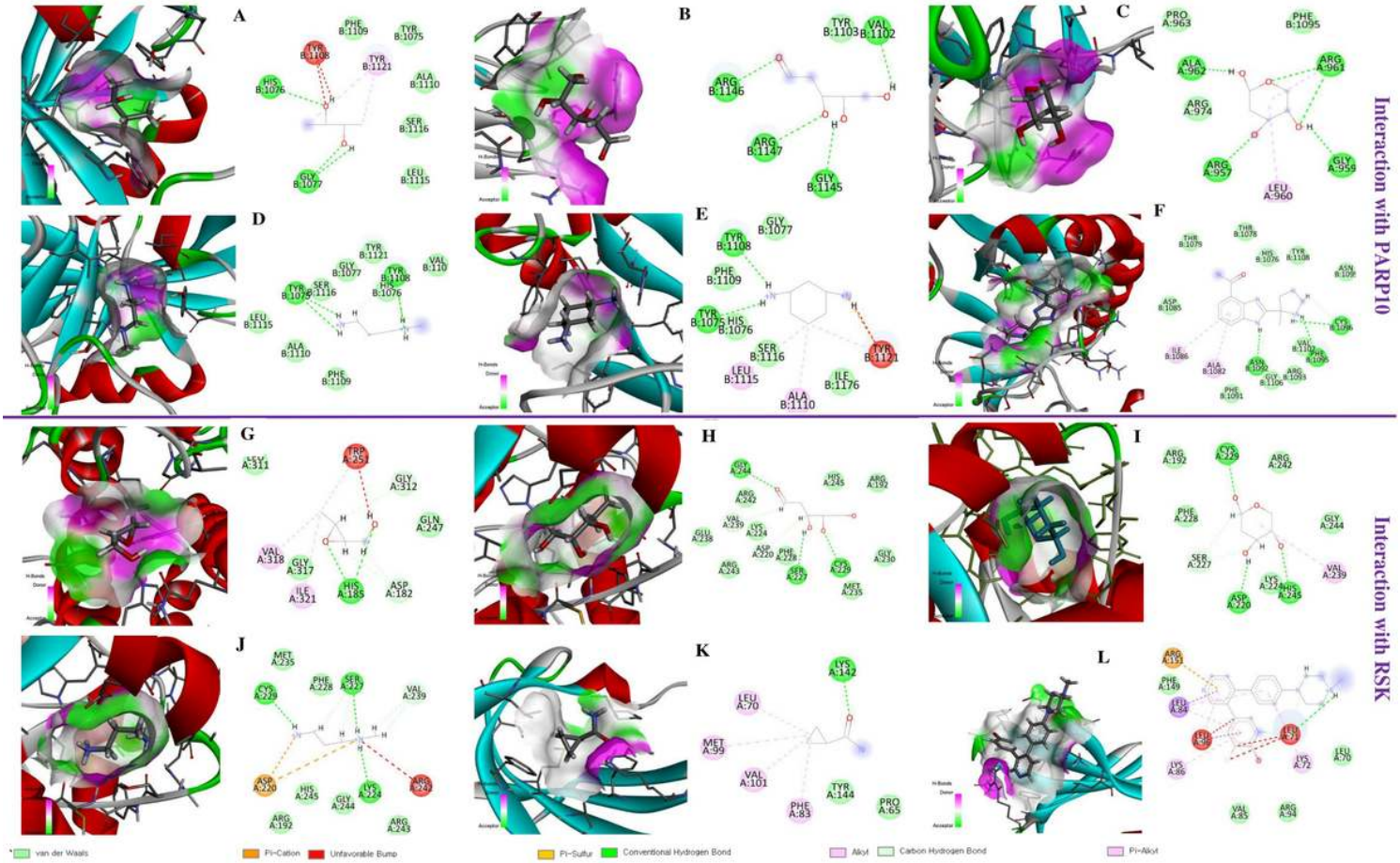

Figure 9

3D and 2D representations of the molecular interactions of selected compounds identified from the aqueous extract of *D. arborea* interacting with PARP10 **(A-F)** and p90 RSK **(G-L). (A)** 2,3-butanediol, **(B)**2-deoxypentose, **(C)** 2-deoxy-alpha-d-ribopyranose, **(D)**1,3-Propanediamine, N-methyl-, **(E)** Cis-cyclohexane-1,3-diamine, **(F)**Veliparib, **(G)** (3-methyl-2-oxiranyl)methanol, **(H)**2-deoxypentose, **(I)** 2-deoxy-alpha-d-ribopyranose, **(J)**1,3-Propanediamine, N-methyl-, **(K)** cyclopropanecarboxamide, **(L)**LJH685.

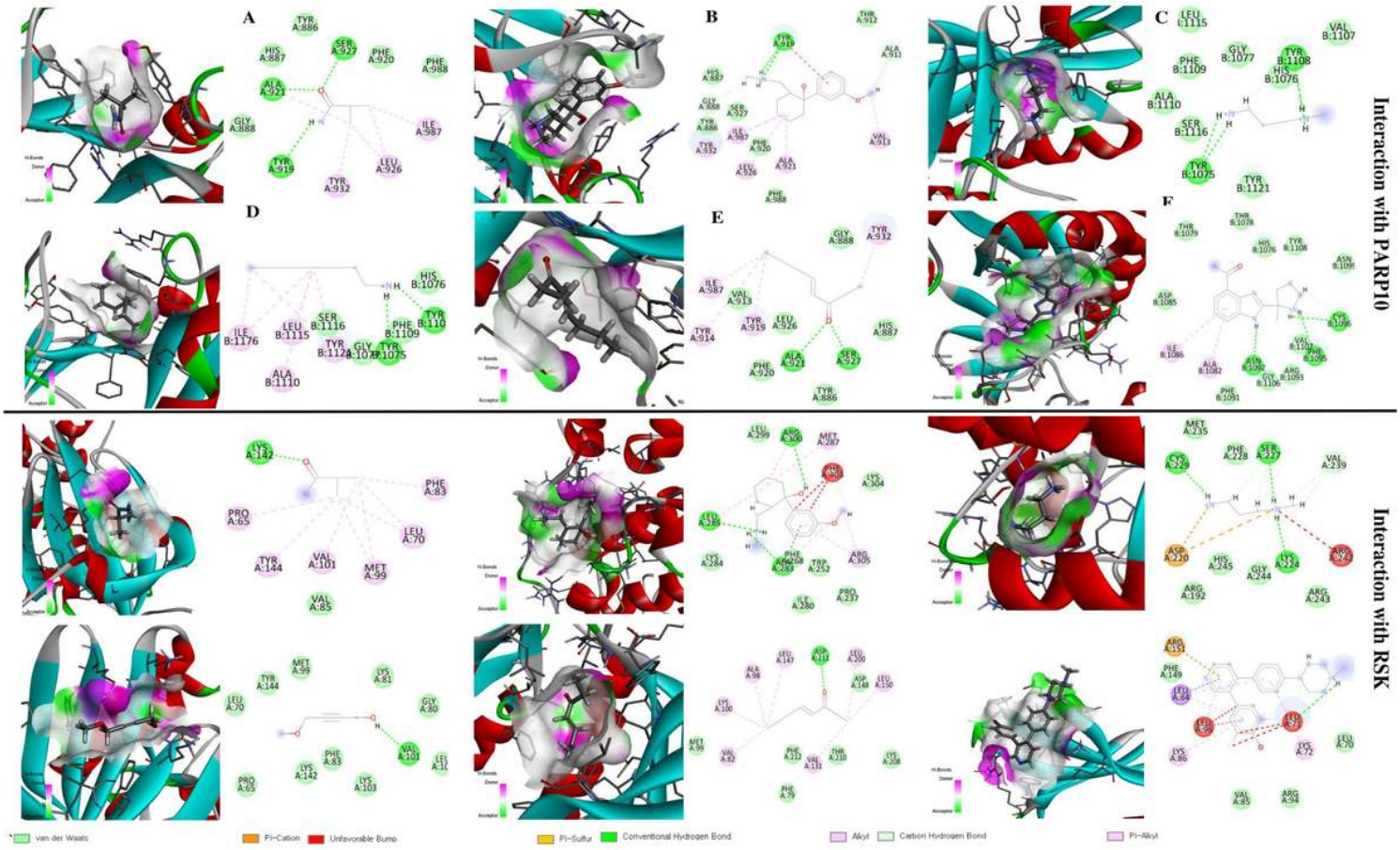

Figure 10

3D and 2D representations of the molecular interactions of selected compounds identified from the aqueous extract of *B. ferruginea* interacting with PARP10 **(A-F)** and p90 RSK **(G-L). (A)** isobutyramide, **(B)**2-[(methylamino)methyl]cyclohexanol, **(C)** N-Methyl-1,3-propanediamine, **(D)**heptylamine, **(E)** 4-octen-3-one, **(F)** Veliparib, **(G)**isobutyramide, **(H)** 2-[(methylamino)methyl]cyclohexanol, **(I)**N-Methyl-1,3-propanediamine, **(J)** 4-methoxy-2-butyn-1-ol, **(K)**4-octen-3-one, **(L)** LJH685.

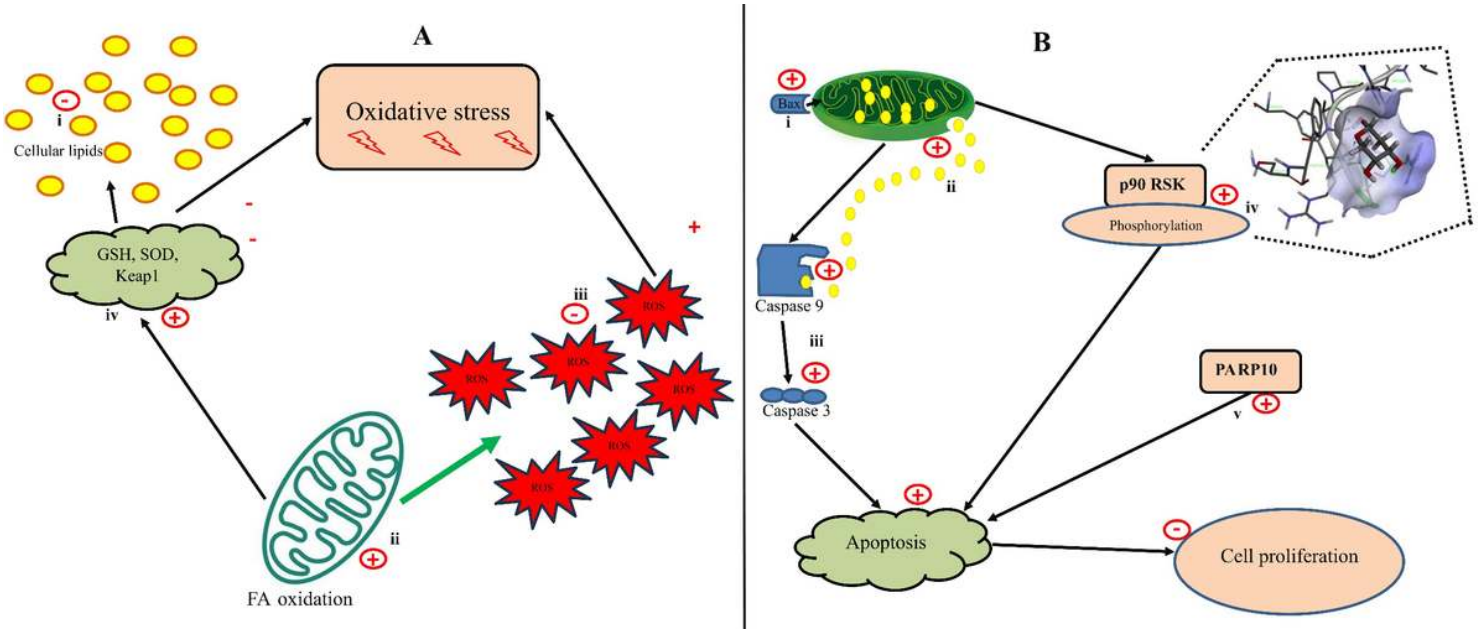

Figure 11

Proposed mechanism of action of *B. ferruginea* **(A) and** *D. arborea* (B) **in the regulation of oxidative stress and cell proliferation, respectively. (A)** *B. ferruginea* could exhibit its potent antioxidant activity by inhibiting the peroxidation of cellular lipids (i), which could promote fatty acid oxidation at the level of mitochondria (ii), resulting in the reduction of ROS and finally leading to the reduction of oxidative stress (iii). In addition, this plant could directly increase the production of antioxidant enzyme and Keap1(iv). **(B).** Bax, cytochrome C and caspases 3/9 are the main proapoptotic factors involved in the intrinsic pathway of apoptosis. *D. arborea* could activate Bax (i), which could enter mitochondria and induce release of mitochondrial cytochrome C (ii). This proapoptotic factor could then activate caspase 3 and 9 (iii), which could promote apoptosis and decrease cell proliferation. 2-deoxy-alpha-d-ribopyranose was the most stable compounds, as it was attached to the active pocket of the protein via 5 conventional hydrogen bonds. This ligand could activate ERK1/2 and phosphorylate p90 RSK (iv), which in turn could increase apoptosis and decrease cell proliferation. Another partway could be via PARP10 phosphorylation. This ligand could directly modulate PARP10 phosphorylation (v), which may promote apoptosis and decrease cell proliferation.

Supplementary Files

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