

Chemical characterization and biological abilities of *Anthocleista djalonensis* collected from two locations of Ivory Coast

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Abstract

In this study, the total phenolic and flavonoid contents, HPLC-DAD detected phytochemicals, antioxidant and enzyme inhibitory potential of methanolic and aqueous (as infusion) extracts of the medicinal plant, *Anthocleista djalonensis* (leaf and stem bark) collected from two locations, Mafiblé and Prikro, in Ivory Coast, were investigated. The ranges of total phenolic and flavonoid contents obtained were 14.17–46.95 mg gallic acid equivalent (GAE)/g and 2.96–34.76 mg rutin equivalent (RE)/g, respectively. Antioxidant abilities in terms of radical scavenging, reducing and metal chelating activity of the extracts in different assays were as follows: DPPH (4.90–48.82 mg trolox equivalent [TE]/g), ABTS (21.05–81.89 mg TE/g), CUPRAC (29.54–122.33 mg TE/g), FRAP (17.53–94.06 mg TE/g) and metal chelating (10.09–28.49 mg EDTAE/g). The extracts of *A. djalonensis* collected from Mafiblé, especially those of stem bark, contained higher level of total bioactive contents compared to Prikro extracts, detected by high-performance liquid chromatography with photodiode-array detection (HPLC-DAD). Only the methanolic extracts irrespective of plant parts/location, showed inhibition against acetylcholinesterase (1.42–2.12 mg galantamine equivalent (GALAE)/g), while only the stem bark methanolic extract of *A. djalonensis* from Mafiblé was found to inhibit butyrylcholinesterase (0.65 mg GALAE/g). Thus, findings from this study could be useful for better application of the medicinal benefits from this plant.

KEYWORDS

Anthocleista djalonensis, antioxidant, enzyme inhibition, HPLC, Ivory Coast, Mafiblé, phytochemicals, Prikro

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1 | INTRODUCTION

Natural products are an integral part of a healthy and sustainable lifestyle and offer a wide range of benefits to individuals and communities. Phytochemicals, for example, have a wide range of biological activities ranging from antioxidants to anti-inflammatory. In this way, they could serve as a protective shield against degenerative and chronic diseases such as diabetes, cancer, and cardiovascular disease (Aware et al., 2022; Hu et al., 2023; Lin et al., 2014; Singla, De, et al., 2023; Singla, Joon, et al., 2023). Given the context, there is a growing interest in the scientific community to study novel natural products.

The genus *Anthocleista* belonging to the family Gentianaceae comprises of 14 species of shrub-like plants and trees dispersed in tropical Africa, Madagascar and on the Comoros. These plants are traditionally used in the treatment of diseases such as diabetes, obesity, hypertension, malaria, typhoid fever, abdominal pain, diarrhea, hyperprolactinemia, jaundice, ulcer, asthma, cancer, wounds, hemorrhoids, chest pains, rheumatism, inflammations, including infertility, sexually transmitted diseases, and skin diseases and also help as an anthelmintic, a laxative, and diuretic (Anyanwu et al., 2015).

Among the different species of this genus, *Anthocleista djalonenis* has attracted particular attention due to its diverse ethnomedicinal uses for managing various ailments in West African subregions. For instance, the root is used as a strong purgative, and also as an antidote against poison, against leprosy, as an emmenagogue, and for healing oedemas and elephantiasis of the scrotum, in Ivory Coast. On the other hand, root decoction is taken to have relief from chest pains, for constipation and against gonococci (Togola et al., 2005). The bark, seeds, and roots of *A. djalonenis* are widely utilised in Nigeria, as an antipyretic, a laxative, and therapy for various stomach disorders and are used in conditions like diabetes and hepatitis (Awah et al., 2010; Okoli & Iroegbu, 2004). In contrast, the aqueous leaf extract of the plant mixed with lemon juice is used in Ghana for curing epilepsy, while in Senegal, it is employed as a diuretic (Okoli & Iroegbu, 2004).

In addition, various scientific studies have confirmed the exceptional medicinal virtues of this plant. In such a study, the hypoglycemic effect of the aqueous stem bark extract of *A. djalonenis* was established by the oral route in normoglycemic and hyperglycemic rabbits (Kroa et al., 2016). Besides, in vitro antiplasmodial assay revealed that the aqueous and ethanol extracts of this plant to inhibit growth of clinical isolates and chloroquinoreistant strains (K1). Moreover, phytochemical screening showed that the extracts to contain largely alkaloids, polyphenols, flavonoids, and polyterpenes (Bla et al., 2020). Furthermore, the leaf extracts of *A. djalonenis* were found to be effective against a range of microorganisms (Akinyemi, 2014; Ojiakor &

EOkoye, 2015; Solomon Okoro, 2017). Besides, the methanol root bark extract of *A. djalonenis* was found to enhance fertility parameters in male rats (Okeke et al., 2019), while in another study, the root extract exerted antiplasmodial and antipyretic activities, suggested to be partly mediated through the chemical constituents of the plant (Akpan et al., 2012). The antiproliferative effect of *A. djalonenis* on human breast cancer cell lines has also been reported (Iwalokun et al., 2021). Accordingly, gathering scientific information on this plant can be useful in the field of phytomedicine research and development.

Indeed, there is also growing evidence of the impact of geographical variations on the chemical constituents as well as the biological activities of plants (AL-Hmadi et al., 2021; Khattak & Rahman, 2015; Liu et al., 2018). Therefore, this study is aimed to assess the phytochemical profile, to determine the quantitative total bioactive contents, along with the antioxidant and enzyme inhibitory effects of infusion and methanolic, leaf and stem bark extracts of *A. djalonenis* collected from two locations in Ivory Coast, Mafibl  and Prikro. Additionally, the chemical profile and biological activities of the extracts obtained from *A. djalonenis* from these two locations will be compared.

2 | MATERIALS AND METHODS

2.1 | Plant materials and extraction

The leaves and stem barks of the plants (*Anthocleista djalonenis*) were collected from two localities (Mafibl  and Prikro) of Ivory Coast in the summer season of 2020. The plant was identified by one botanist coauthor (Dr. Ouattara Katinan Etienne). Voucher specimens were deposited at the herbarium in Selcuk University. The plant materials were cleaned thoroughly by washing them with tap water and rinsing them with distilled water to remove soil and contaminants. The aerial parts were then separated and dried for 10 days in a well-ventilated (humidity: 10%–12%) and shaded environment at room temperature. The dried materials were ground into powder using a Retsch SM-200 laboratory mill and extracted within the same week. The powdered plant material was stored in a cool, dark, and well-ventilated area at around 20°C.

We used two solvents (methanol and water) in the preparation of plant extracts. The maceration method was chosen for methanol extracts, and 10 g of plant material was mixed with 200 mL of methanol (100%) for 24 h at room temperature. The mixtures were then filtered with Whatman 1 filter paper, and the solvents were removed with a rotary-evaporator. Regarding water extract, it was prepared as a traditional infusion and 10 g of plant material was waited in 200 mL of boiled water for 15 min. The mixture was subsequently filtered and

lyophilized for 48 h. All extracts were kept at 4°C until analysis.

2.2 | HPLC-MS/MS triple quadrupole analysis

Following a previous procedure with modifications (Mahomoddally et al., 2021), the dried extracts' content of selected bioactive compounds, including phenolic acids, derivatives of phenolic acids, flavonoids, xanthenes, and iridoids, was analyzed. The dried extracts were individually dissolved in methanol (5 mg/mL), and each sample was filtered through a 0.2 µm filter. An Agilent 1290 Infinity series and a Triple Quadrupole 6420 from Agilent Technology with an electrospray ionization (ESI) source operating in negative mode were used for the present study. All analytical parameters are given in the Supporting Information materials.

Determination of total phenolic, flavonoid and antioxidant, and enzyme inhibitory effects

Total phenolic content (TPC), total flavonoid content (TFC), DPPH radical scavenging, ABTS radical scavenging, cupric reducing antioxidant capacity (CUPRAC), ferric reducing antioxidant power (FRAP), metal chelating activity (MCA), phosphomolybdenum (PBD), inhibition of acetylcholinesterase (AChE), butyrylcholinesterase (BChE), tyrosinase, amylase, and glucosidase assays were performed as previously described (Grochowski et al., 2017; Uysal et al., 2017). Gallic acid and rutin were used as standard compounds to evaluate the levels of total phenolic and flavonoid content in the extracts. Trolox (for DPPH, ABTS, CUPRAC, FRAP, and PBD) and EDTA (for metal chelating assay) were used as standard compounds in the antioxidant assays. Galanthamine (for AChE and BChE), kojic acid (for tyrosinase) and acarbose (for amylase and glucosidase) were standard enzyme inhibitors in the enzyme inhibition assays. Each sample was processed in triplicate. All experimental details are given in the Supporting Information material.

2.3 | Molecular docking

Crystallographic structures of the target enzymes: AChE (PDB ID: 6O52) (Gerlits et al., 2019), BChE (6EQP) (Rosenberry et al., 2017), amylase (6TP0) (Božić et al., 2020), tyrosinase (6JU7) (Fujieda et al., 2020), and Glucosidase (7KBJ) (Karade et al., 2021) were retrieved from the protein data bank (<https://www.rcsb.org/>). All water molecules were removed, and missing Hydrogen atoms were added. The resulting protein structures were prepared at physiological pH of 7.4. During this processing, atom bond orders were corrected, and missing atoms were added using Biovia Discovery Studio (DS) (Accelrys Software Inc, 2012).

The three-dimensional structure of each ligand was downloaded from the PubChem database (pubchem.ncbi.nlm.nih.gov/) and their geometry was optimized using the “lig prep” toolkit in Biovia DS.

AutodockTools program (<https://autodock.scripts.edu>) (Morris et al., 2009) was used to generate a docking grid file using the coordinates of the cocrystal ligand in each PDB structure. Autodock 4.2, utilizing the Lamarckian genetic algorithm, was used to generate distinct ligand conformers, which were docked to the active site of each enzyme. A conformer with the lowest binding energy was examined for good binding pose using Biovia DS Visualizer.

2.4 | Data analysis

Data are presented as mean ± standard deviation. One-way analysis of variance with Tukey's post-hoc test was achieved; $p < 0.05$ was considered statistically significant. Cluster image map (CIM) analysis were done on chemical compounds, antioxidant, and enzyme inhibitory datasets respectively. Prior doing CIM analysis, each data set was scaled. Then Pearson correlation coefficient between the chemical compounds and the antioxidant and enzyme inhibitory activity were calculated. Pearson's coefficient higher than 0.7 was considered statistically significant. All analyses were done under R v 4.1.2 software.

3 | RESULTS AND DISCUSSION

3.1 | Chemical composition

Natural antioxidants in medicinal plants are responsible for inhibiting the damaging effects of oxidative stress. These plants contain polyphenols that act as free radical scavengers and reduce oxidative stress and thus, may be an alternative remedy to cure various human diseases linked to oxidative stress such as rheumatoid arthritis, cardiovascular and neurological diseases (Phuyal et al., 2020; Pizzino et al., 2017; Stefanucci et al., 2018; Uysal et al., 2019; Zengin et al., 2018). Polyphenols are a renowned group of phenolic systems that are characterized by at least two phenyl rings and one or more hydroxyl substituents (Singla et al., 2019). Hence, as a preliminary investigation, the total phenolic and flavonoid contents of the studied extracts were determined using spectrophotometric/colorimetric assays.

Furthermore, the choice of solvents used is an important aspect to consider when extracting phytochemicals from plants. In this study, methanol and water were used. In fact, it has previously been reported that *A. djalensis* methanol and aqueous extracts yielded the best extraction efficiency of phytochemicals and thus, the optimum extraction of desirable phytochemicals from *A. djalensis* could be obtained by using either methanol

and water (Popoola, 2020). Consequently, methanol and water were chosen as solvents in the present study.

For the extracts of *A. djalonensis* from Mafibl  location, methanolic leaf extracts yielded higher TPC (46.95 mg gallic acid equivalent [GAE]/g) and TFC (34.76 mg rutin equivalent [RE]/g) (Figure 1). As regards the extracts of *A. djalonensis* from Pri kro location, both extracts of stem bark were found to have higher TPC (MeOH = 22.81 mg GAE/g; Infusion = 23.02 mg GAE/g) while only methanolic leaf extracts recorded the strongest TFC (14.17 mg RE/g). In the literature, several authors reported different levels of total phenolic and flavonoid contents of the members of *Anthocleista* including *A. djalonensis*. For example, Patrick and Okeke (2019) reported that total phenolic and flavonoid contents of the methanol extract of *A. djalonensis* roots were 207.93 mg GAE/g and 100.6 mg quercetin equivalent (QE)/g, respectively, which was higher than who reported on our study. In another study by Awah et al. (2010), the total flavonoid content in the methanol extract of leaves of *A. djalonensis* were found to be 48.52 mg RE/g, which was higher than in our tested leaf extracts. However, the total phenolic level of ethanolic extract of *A. djalonensis* root barks (10.1 mg GAE/g) was lower than that of our tested extracts (14.17–46.95 mg GAE/g) in a previous study by Monon Kone et al. (2022). The differences could be explained by geographical and climatic factors including altitude, rainfall, or plant collection stages. In fact, numerous reports have been published on the influence of environmental factors on the biosynthesis of polyphenols (Jaakola & Hohtola, 2010; Sampaio et al., 2011). Besides, results from other studies have suggested the importance of geographic origin, with temperature and weather conditions, as the chief drivers affecting the accumulation of phenolics in plants

(Liu et al., 2018). In our study, the total content of phenols and flavonoids clearly changed in two locations in Ivory Coast.

The study of plant phytochemicals is definitely an essential pipeline in pharmaceutical discovery. Therefore, in this study, high-performance liquid chromatography with photodiode-array detection (HPLC-DAD) was used to determine the quantitative contents of selected phytochemicals. Overall, extracts of *A. djalonensis* collected from Mafibl  were found to contain higher total bioactive compounds compared to the Pri kro extracts (252.60–684.32 $\mu\text{g/g}$ and 84.20–282.59 $\mu\text{g/g}$, respectively) (Table 1). Five compounds were commonly found in all extracts: loganic acid (0.18–222.24 $\mu\text{g/g}$), swertiamarin (1.76–96.50 $\mu\text{g/g}$), sweroside (7.53–418.60 $\mu\text{g/g}$), p-coumaric acid (0.09–2.22 $\mu\text{g/g}$), and 3,5-dicaffeoylquinic acid (0.09–0.79 $\mu\text{g/g}$) (Table 2). Interestingly, the extracts were found to be rich in iridoids such as sweroside which has been found to possess important anti-inflammatory activities (Wang et al., 2019; Zhang et al., 2019). Moreover, loganic acid present in high amounts in stem bark extracts of *A. djalonensis* from Mafibl , has been previously reported to exert strong free radical scavenging activity and notable cyto-protective effect (Abirami et al., 2022). In brief, the stem bark methanolic extract of Mafibl  yielded the highest total bioactive contents, followed by the stem bark-infusion and leaves-methanol extract. Stem bark-methanolic extract from Pri kro also showed higher total bioactive content relative to the other extracts of *A. djalonensis* from Pri kro. Besides, the cluster image map analysis on the compound's data sets revealed two clusters (Figure 2). Cluster I was represented by the stem bark methanolic, stem bark-infusion, and leaves-methanol extract of Mafibl  while Cluster II contained the remain extracts. Thus, overall, the stem bark extracts, especially the methanolic extracts were

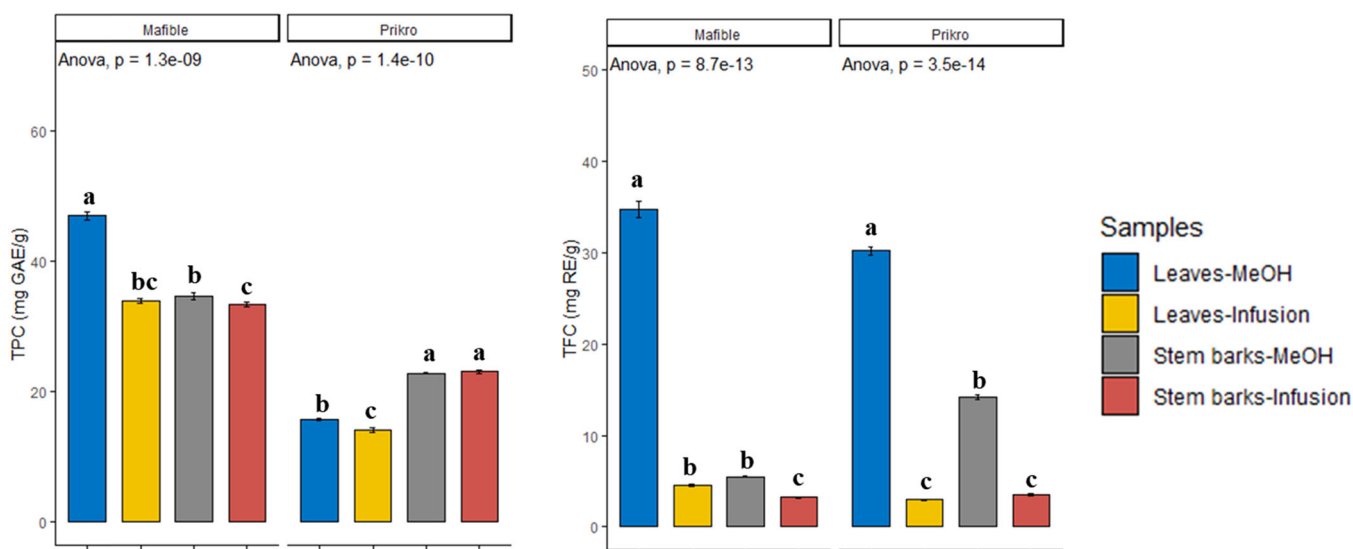


FIGURE 1 Total phenolic and flavonoid contents of the tested extracts. GAE, gallic acid equivalent; RE, rutin equivalent; TFC, total flavonoid content; TPC, total phenolic content.

TABLE 1 Bioactive compounds content ($\mu\text{g/g}$ of dried weight extract) found in various extracts of *A. djalensis*.

No.	Compound	Mafibl�				Pikro			
		Leaves-MeOH	Leaves-infusion	Stem Barks-MeOH	Stem Barks-infusion	Leaves-MeOH	Leaves-infusion	Stem Barks-MeOH	Stem Barks-infusion
1	Shikimic acid	n.d.*	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
2	Gallic acid	0.22	0.05	0.22	0.08	0.10	n.d.	0.06	n.d.
3	Loganic acid	94.72	74.38	222.24	140.20	14.02	9.41	0.73	0.18
4	3-Caffeoylquinic acid	1.63	0.68	1.40	0.93	n.d.	n.d.	1.76	n.d.
5	Swertiamarin	54.73	36.53	3.15	1.76	96.50	65.22	45.46	30.38
6	(+)-Catechin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
7	Delphinidin-3,5-diglucoside	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
8	Sweroside	188.83	130.91	418.60	258.39	8.35	7.53	207.72	130.91
9	5-Caffeoylquinic acid	2.81	0.89	3.40	1.20	2.35	n.d.	11.98	0.58
10	Vanillic acid	n.d.	n.d.	19.00	9.01	0.59	0.59	5.48	2.35
11	Caffeic acid	1.30	0.10	5.44	3.19	0.82	n.d.	1.12	n.d.
12	(-)-Epicatechin	n.d.	n.d.	n.d.	n.d.	0.13	0.20	0.51	0.40
13	Syringic acid	0.26	n.d.	0.52	0.57	n.d.	n.d.	0.47	0.10
14	p-Coumaric acid	1.63	1.15	2.22	1.46	1.40	0.37	0.56	0.09
15	Ferulic acid	n.d.	0.14	1.14	0.71	1.21	0.11	0.68	0.64
16	3,5-Dicaffeoylquinic acid	0.79	0.26	0.43	0.26	0.32	0.29	0.18	0.09
17	Naringin	n.d.	0.18	n.d.	n.d.	0.70	0.44	5.82	1.37
18	Rutin	3.01	0.88	3.41	1.77	0.09	n.d.	0.04	n.d.
19	Hyperoside	0.50	0.14	0.58	0.28	0.24	0.04	n.d.	n.d.
20	Resveratrol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
21	Amarogentin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
22	Kaempferol-3-O-glucoside	0.02	0.03	n.d.	n.d.	0.35	n.d.	0.03	0.01
23	Quercitrin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
24	Quercetin	0.03	n.d.	0.04	n.d.	n.d.	n.d.	n.d.	n.d.
25	Isogentisin	53.28	6.27	2.54	1.11	0.04	0.02	0.01	n.d.
Total bioactive compounds		403.76	252.60	684.32	420.93	127.23	84.20	282.59	167.09

Note: % relative standard deviation ranged from 3.4 to 11.1% for all samples.

Abbreviation: n.d., not detectable.

TABLE 2 Calculated binding energy values of the dominant bioactive compounds various extracts of *Anthocleista djalensis*.

Compound	AChE	BChE	Tyrosinase (kcal/mol)	Amylase	Glucosidase
Loganic acid	-11.35	-7.88	-6.44	-8.27	-9.04
Swertiamarin	-9.98	-8.13	-5.34	-8.00	-7.44
Sweroside	-8.31	-8.56	-3.74	-7.98	-9.40

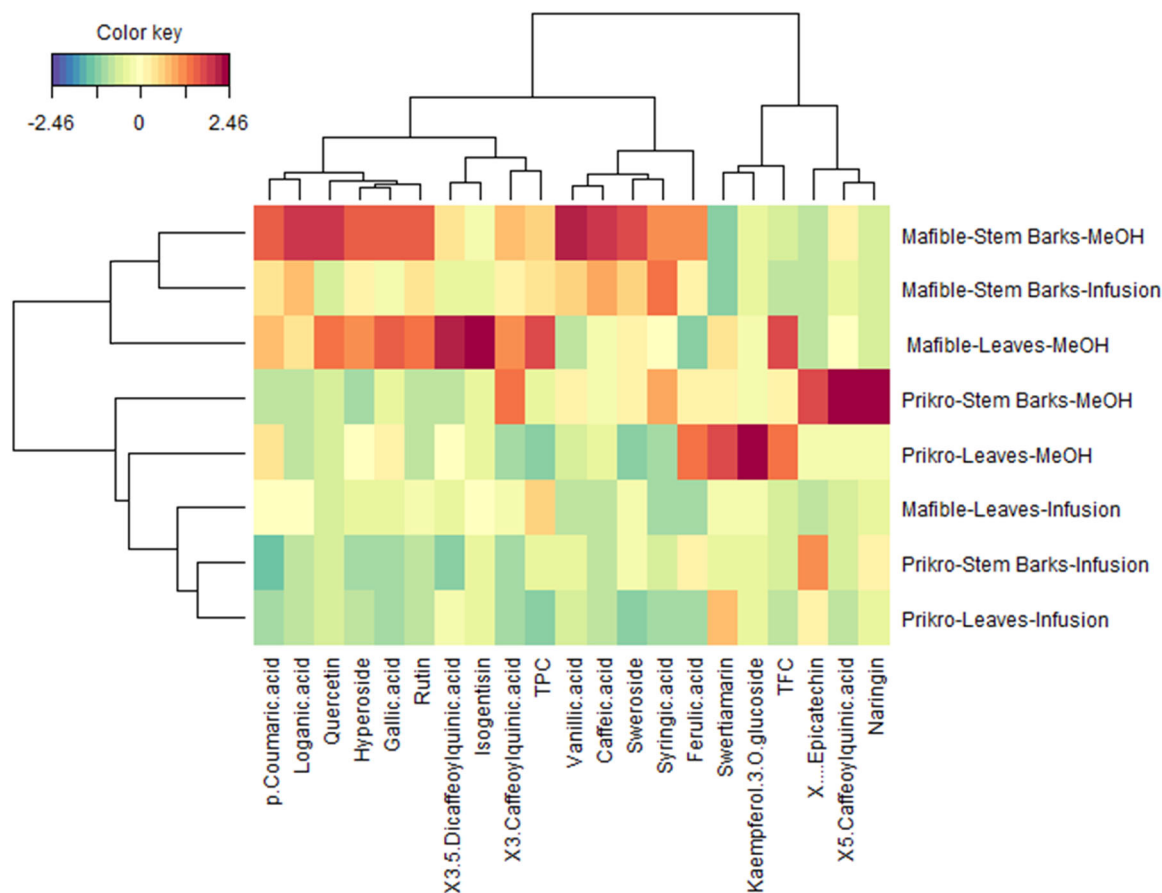


FIGURE 2 Clustered image map analysis (Red color: high content and blue color: low content) on phytochemical data set of *A. djalonenensis* extracts.

found to yield richer total bioactive contents compared to extracts of leaves prepared by infusion method. Other researchers have also conducted phytochemical analysis on *A. djalonenensis*. For instance, phytochemical screening of the methanol leaf extract of *A. djalonenensis* revealed the presence of flavonoids, saponins, alkaloids, terpenoids, steroids and tannins (Lawal et al., 2020). Similarly, results reported by Ojiakor and EOkoye (2015) showed that both ethanolic and aqueous extracts of *A. djalonenensis* contain alkaloids, tannins, flavonoids, cardiac glycoside, saponin as well as reducing sugar. Additionally, phytochemical screening of four solvents (methanol, aqueous, ethyl acetate, and hexane) extracts of *A. djalonenensis*, were determined earlier by Popoola (2020), indicating the presence of all the phyto-compounds in the methanol extract, while the availability of different phytochemicals such as flavonoids, alkaloids, saponin, phenol, tannin, cardiac glycoside, and terpenoids varied in the other extracts.

3.1.1 | Antioxidant capacity

In the present investigation, the extracts of *A. djalonenensis* from Mafibl  showed better antioxidant potential, both in

terms of radical scavenging and reducing activities compared to those obtained from Prikro's *A. djalonenensis* (Figure 3). Mafibl  extracts demonstrated scavenging abilities in the range of 41.12–48.82 mg TE/g (DPPH) and 66.95–81.89 mg TE/g (ABTS), respectively. While Prikro extracts possessed scavenging abilities in the range of 4.90–22.13 mg TE/g (DPPH) and 21.05–59.93 mg TE/g (ABTS). In the CUPRAC, FRAP, and PBD assays, leaf methanolic extract of *A. djalonenensis* from Mafibl  showed the highest activity (CUPRAC = 122.33 mg TE/g; FRAP = 94.06 mg TE/g and PBD = 1.68 mmolTE/g). In contrast, the leaf infusion extract demonstrated the highest levels of capability in the MCA assay (24.09 mg EDTA equivalent [EDTAE]/g). As regards extract of *A. djalonenensis* from Prikro, the methanolic stem bark extract displayed the highest activity of FRAP (50.47 mg TE/g) and metal chelating (28.49 mg EDTAE/g), however, both stem bark extracts acted as better Cu^{+2} reducing power (MeOH = 52.55 mg TE/g; Infusion = 50.07 mg TE/g). While the best total antioxidant capacity was found in the methanolic extract of leaf (1.26 mmol TE/g) and stem bark (1.26 mmol TE/g). Afterward, clustered image map was plotted to visualize the similarities or differences between the samples by simultaneously considering all the

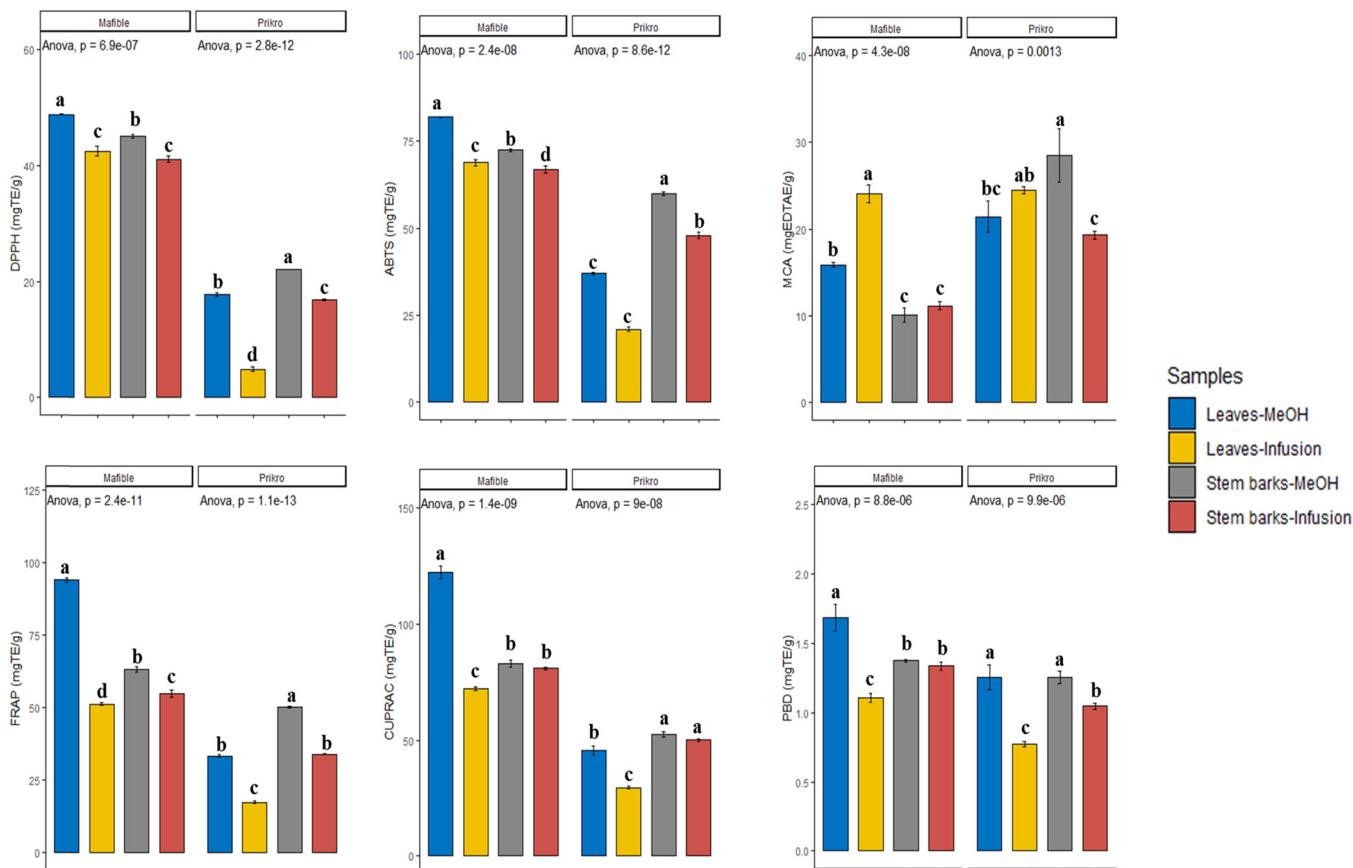


FIGURE 3 Antioxidant properties of the tested extracts. EDTAE, EDTA equivalent; MCA, metal chelating assay; PBD, phosphomolybdenum; TE, trolox equivalent.

antioxidant assays. As can be seen in Figure 4A two clusters were obtained; the stem bark methanolic, stem bark-infusion, and leaves-methanol extract of Mafible were grouped together and they presented overall the best antioxidant activities. This classification is identical to that carried out previously on the chemical compounds database. In a previous study by Patrick and Okeke (2019), the DPPH scavenging ability of various extracts from roots of *A. djalonenensis* were tested and, consistent with our results, the best radical scavenging ability was provided by methanol extract. Similarly, Awah et al. (2010) reported significant DPPH scavenging ability for methanol extract of *A. djalonenensis* leaves. However, Ngwoke et al. (2018) were investigated the DPPH scavenging ability of various extracts from stem barks of *Anthocleista nobilis* and the best ability was found in the ethyl acetate with the lowest IC_{50} (220 μ g/mL). In the study of Ezirim et al. (2019), phytochemical analysis of root extracts of *A. djalonenensis* also showed that phenol and flavonoid constituents were higher in the methanol than in the aqueous ethanol extract and also had higher antioxidant activity. Therefore, this is in agreement with the findings obtained herein, showing methanol to be a better solvent to yield higher phytochemical content and antioxidant potential.

In the current study, the obtained antioxidant results could be explained by the presence of some compounds. In fact, a significant positive correlation was found between DPPH and gallic acid, loganic acid, p-coumaric acid, rutin, hyperoside (Figure 4B). Similarly, ABTS was positively linked to sweroside, rutin, and 3-Caffeoylquinic acid while FRAP, CUPRAC, and PBD were positively bound to gallic acid, rutin, hyperoside, and 3,5-dicaffeoylquinic acid. In addition, a positive significant relationship was found between 3-Caffeoylquinic acid-FRAP, 3-Caffeoylquinic acid-PBD, isogentisin-FRAP, and isogentisin-CUPRAC. As far as our literature survey could as certain, the antioxidant properties of these molecules have already been demonstrated and reported in the literature (Abirami et al., 2022; Alcázar Magaña et al., 2021; Badhani et al., 2015; Boz, 2015; Enogieru et al., 2018; Gao et al., 2019; Li et al., 2021).

3.1.2 | Enzyme inhibitory effects

It is suggested that deficits in the cholinergic pathways of the brain are accountable for several of the cognitive and behavioral variations experienced by Alzheimer's disease (AD) patients. Since direct replacement of acetylcholine may not be viable due to associated side

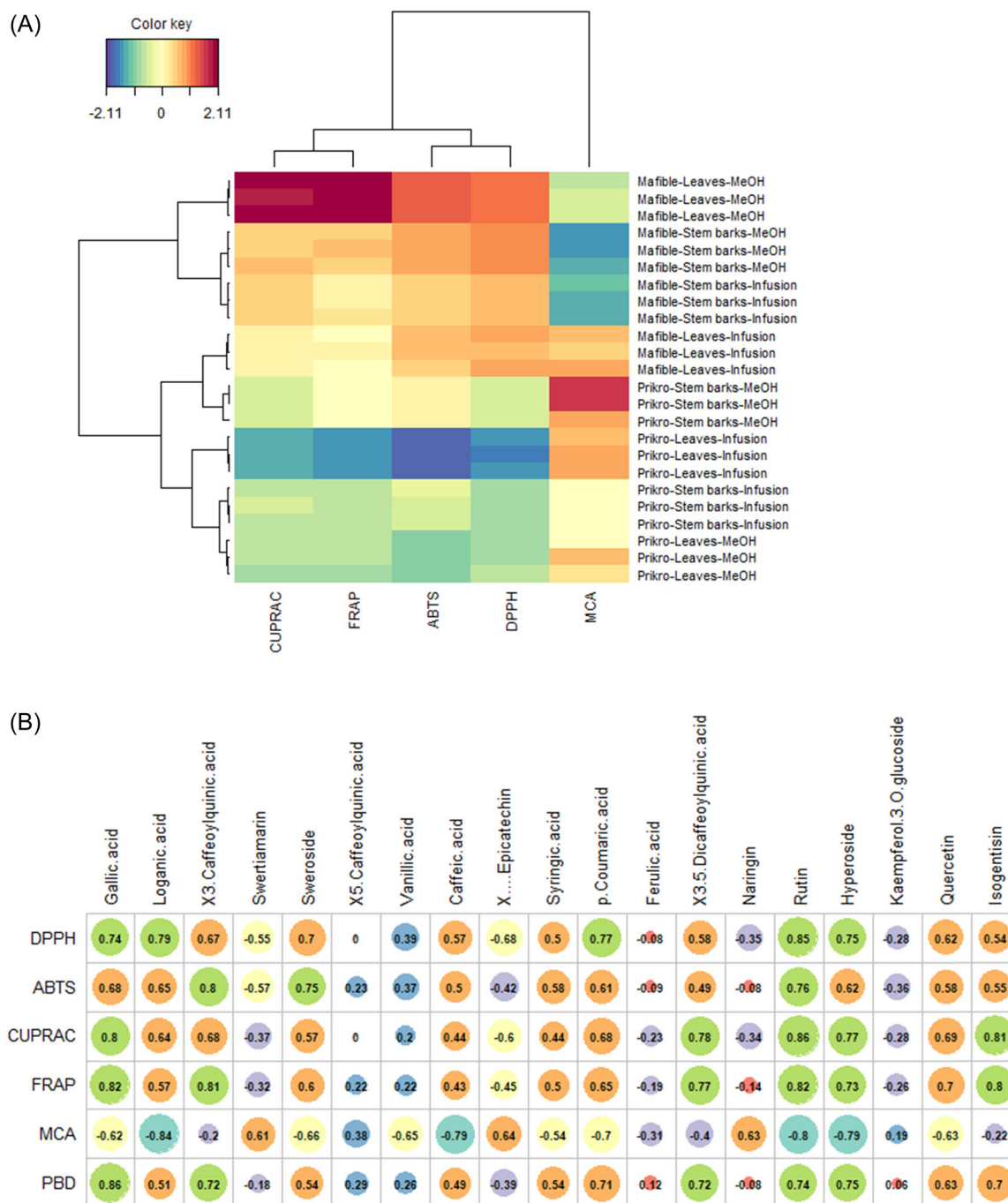


FIGURE 4 Clustered image map analysis (Red color: high activity and blue color: low activity) on antioxidant activity data set of *A. djalonensis* extracts (A) and relationship between antioxidant activities and individual phytochemicals (B).

effects, other drug remedies have been established, focusing on enhancing acetylcholine by means of other mechanisms that can improve symptoms linked to AD. Cholinesterase inhibitors are indeed the most studied, of these drugs. They act to rise cholinergic transmission by inhibiting cholinesterase enzymes that cause break down of acetylcholine. Hence, the administration of such inhibitors results in a surge in the amount of acetylcholine molecules, available to interact with the postsynaptic acetylcholine receptors and as a result,

leads to an increase in CNS acetylcholine activity (Lee et al., 2011).

Interestingly, herein, none of the infusion extracts from Mafibl  and Prikro showed anticholinesterase activity and only the methanolic extracts were found to display anti-AChE activity (1.42–2.12 mg GALAE/g) (Figure 5). On the other hand, only stem bark methanolic extract from Mafibl  was found to inhibit BChE (0.65 mg GALAE/g) (Figure 5). The anti-AChE activity of other *Anthocleista* species have also been tested. For

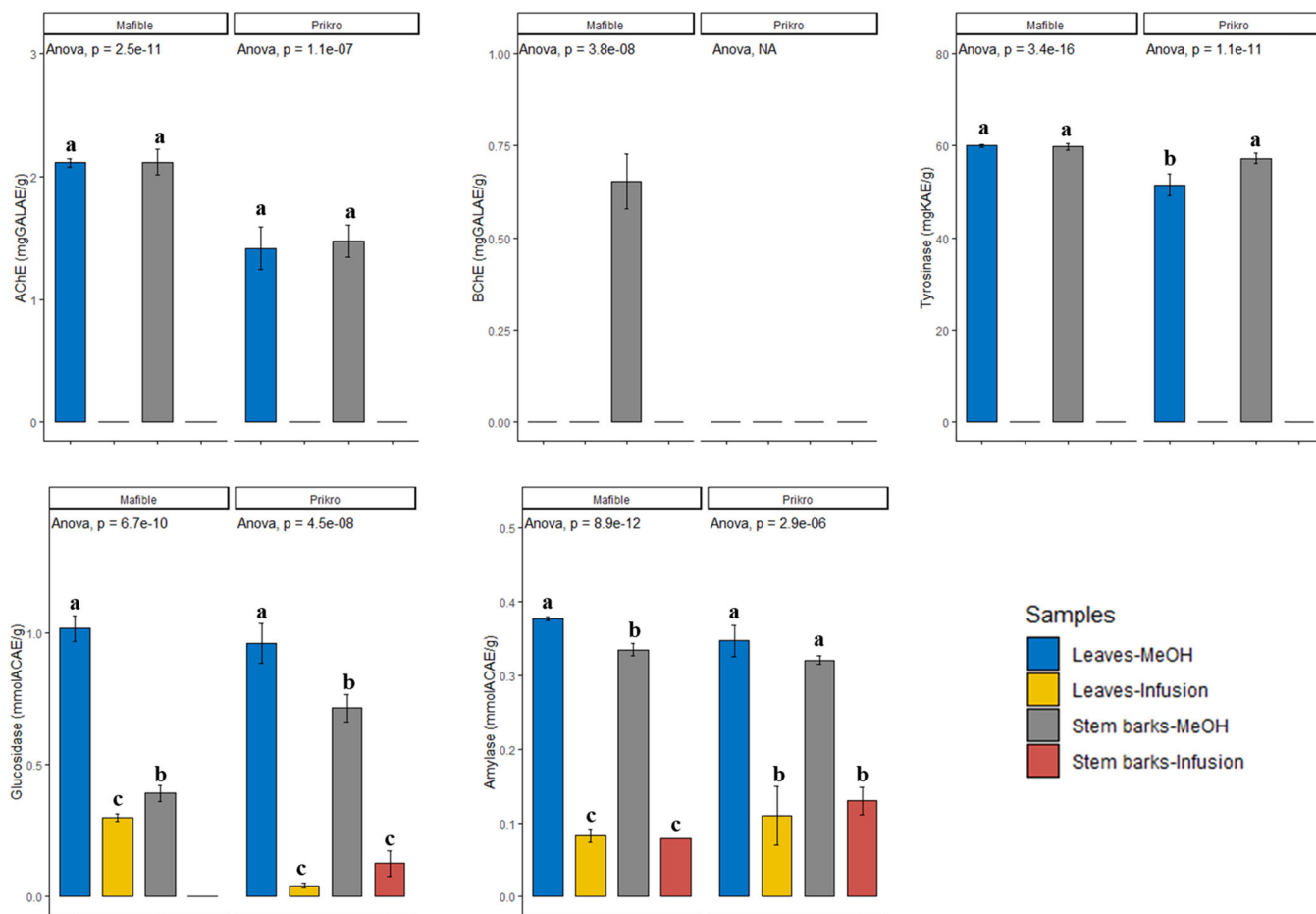


FIGURE 5 Enzyme inhibitory properties of tested extracts. ACAE, acarbose equivalent; GALAE, galantamine equivalent; KAE, kojic acid equivalent.

instance, the solvent fractions (*n*-hexane, dichloromethane, ethyl acetate, and *n*-butanol) from the crude leaf extract of *Anthocleista vogelii* and isolated compounds were tested for their anti-AChE activity. In their study, the best AChE inhibition was provided by *n*-butanol extract with the value of IC_{50} 564.58 μ g/mL (Ajayi et al., 2019).

The activity of the enzyme tyrosinase determines the synthesis of melanin. Hence, inhibiting tyrosinase is one of the most efficient ways to resolve excess pigmentation (Song et al., 2022). Disorder in melanin production has been found to be responsible for a variety of skin diseases such as hyperpigmentation, vitiligo, lentigo, and skin cancer. On the other hand, the appearance of brown pigments in fruits and vegetables owing to tyrosinase activity is a leading cause of postharvest losses. Therefore, tyrosinase inhibitors are highly valuable in the pharmaceutical, cosmetics, and food industries (Deri et al., 2016). Although researchers are working to find effective tyrosinase inhibitors, most of them are limited, due to cell mutation and cytotoxicity (Song et al., 2022). In this context, many studies have highlighted the tenacity of plants and their derived products against tyrosinase and

hence they are greatly used as natural antityrosinase inhibitors (Riaz et al., 2021). In this study, the same inhibitory pattern of the extracts was noted with tyrosinase as with AChE, whereby only the methanolic extracts from both localities acted as tyrosinase inhibitors (51.55–60.03 mg KAE/g) (Figure 5). This could be mostly due to better total bioactive contents yielded and relatively higher antioxidant activity in the methanolic extracts than in the infusion extracts. Hence, it could be suggested that tyrosinase inhibition was mediated by the active compounds in the methanolic extracts. To the best of our knowledge, there is no scientific report on the tyrosinase inhibitory properties of the member of the genus *Anthocleista*, therefore our article is the first report and may open a new horizon for the cosmeceutical potential of the genus *Anthocleista*.

Type 2 diabetes is one of the most prevalent metabolic diseases worldwide and is characterized by elevated postprandial glucose levels. It has been discovered that inhibitors of the enzymes-amylase and -glucosidase slow glucose release from starch and oligosaccharides, thereby delaying glucose absorption and causing a reduction in postprandial blood glucose levels. Given that the existing

inhibitors of these enzymes, such as acarbose, used to treat type 2 diabetes have been linked to gastrointestinal side effects, the search for new and safer drugs is regarded as a hot area of research (Proença et al., 2022). Remarkably, phenolic compounds widely distributed in the Kingdom Plantae offer a vast range of possibilities as amylase and glucosidase inhibitors (Ademiluyi et al., 2015; Apostolidis & Lee, 2010; Nair et al., 2013). In the current study, the methanol extracts exhibited stronger amylase and glucosidase inhibitory properties in each plant parts. The methanol extract of leaves displayed stronger amylase inhibitory properties than stem barks. The best amylase and glucosidase inhibition effect was provided by the methanol extract of leaves from Mafible location (0.38 and 1.02 mmol ACAE/g). The antidiabetic properties of *A. djalonensis* have also been investigated and confirmed in other studies using in vivo and in vitro models (Okokon et al., 2012). For example, in a previous study by Olubomehin et al. (2013), the leaves extract of *A. djalonensis* had a stronger amylase inhibitory ability than stem bark and roots, consistent with our presented results. In another study by Anyanwu, Iqbal, et al. (2019), the inhibitory effect of *A. djalonensis* were found to be IC₅₀: 51.60 and 5.86 µg/mL for amylase and glucosidase, respectively.

Indeed, in the present study, the extracts showed differential antienzymatic profile, but clearly, the infusion extracts were weak enzyme inhibitors in the present study. Clustered image map analysis showed that the infusion extracts were distinguished from the methanolic extracts (Figure 6A). This may be due to the absence of specific compounds in the infusion extracts that were extracted by the methanol. To achieve this, the Pearson correlation coefficient was calculated to explore the relationship between the compounds and bioactivities. As reported in Figure 6B, BChE activity varied positively depending on loganic acid, sweroside, vanillic acid, caffeic acid, and quercetin. However, AChE activity was positively linked to gallic acid and quercetin. Gallic acid, a natural phenolic compound found in medicinal plants, is reported to have therapeutic activity in neurophysiological and diabetes mellitus disorders (Kahkeshani et al., 2019). Similarly, neuroprotection by a flavonoid quercetin has been reported in several in vitro studies (Khan et al., 2019). In a study by Liao et al. (2022), quercetin showed significant AChE inhibitory activity and the double bond at positions C2 and C3 in quercetin structure played a key role in the inhibition of AChE. In another study by Kim et al (2011), gallic acid exhibited stronger AChE inhibitory effect when compared with catechin and epicatechin. In addition, although no significant relationship was found between swertisin and AChE, swertisin was found to exhibit better AChE inhibitory activity with IC₅₀ of 32.09 µg/mL than the standard eserine with IC₅₀ of 56.09 µg/mL (Ajayi et al., 2019). Similarly, only gallic acid seemed involved in tyrosinase and amylase activities. As a insight into the structure, the numbers of hydroxyl groups in the phenolic ring could be important to inhibit

amylase and tyrosinase and this fact has been reported in previous studies (Kim & Uyama, 2005; Kim et al., 2011).

3.2 | Molecular modelling

Note that only loganic acid, swertiamarin, and sweroside are present in high amounts in the different extracts tested. These individual components in the extract contributed to the overall enzyme inhibitory activities. For example, according to the literature, sweroside was shown to be moderately active against glucosidase (IC₅₀ = 40.28 ± 0.063 µg/mL) (Anyanwu, Onyeneke, et al., 2019). At varying concentrations, swertiamarin inhibited both amylase and glucosidase (Ahamad et al., 2016). Loganic acid demonstrated inhibitory activity against BChE with IC₅₀ of 1.466 ± 0.103 mmol/L (Wang et al., 2021). However, to the best of our knowledge, the inhibitory activity data of these compounds against all the studied enzymes are not available. Therefore, a docking approach was used to predict their activity since their contents are high in the extracts. Although molecular docking is not highly accurate in terms of predicting binding affinity (Weako et al., 2020), the method helps greatly in determining the ligand binding pose and aids in rationalizing the observed activity of plant extracts (Eltayeb et al., 2023).

The binding energy values of each of the dominant bioactive compounds in the various extracts of *A. djalonensis* are tabulated (Table 2). All the studied compounds were predicted to show binding potential to AChE, BChE, tyrosinase, amylase, and glucosidase. Hence, the protein–ligand interaction details for some selected compounds are shown in Figure 7. In all the compounds, H-bonds are the major contributor to the interaction with the residues in the active site of the target enzymes. In addition, hydrophobic contacts, and several van der Waals interactions allowed the ligands to strongly bind to the channels. Loganic filled up the cavity of AChE by forming multiple H-bonds with polar amino acid residues lining the pocket via its multiple hydroxyl groups, formed a couple of interaction near the entrance to the channel, and several van der Waals interaction all over the active site (Figure 7A). Sweroside bound strongly to BChE, mainly via H-bonds as well, and a couple of van der Waals interactions (Figure 7B). Tyrosinase was modestly bound by loganic acid via a H-bonds and a couple of van der Waals interactions with residues deep inside the narrow channel (Figure 7C). Swertiamarin, via its multiple hydroxyl groups, formed multiple H-bonds and van der Waals interactions with amylase tunnel (Figure 7D). However, sweroside bound to glucosidase mainly via hydrophobic interactions, 2 H-bonds, and several van der Waals interactions (Figure 7E).

Overall, the molecular docking results corroborate the enzyme inhibitory activity data even though the experimental value of each compound against each enzyme was not well reproduced. Nonetheless, the goal

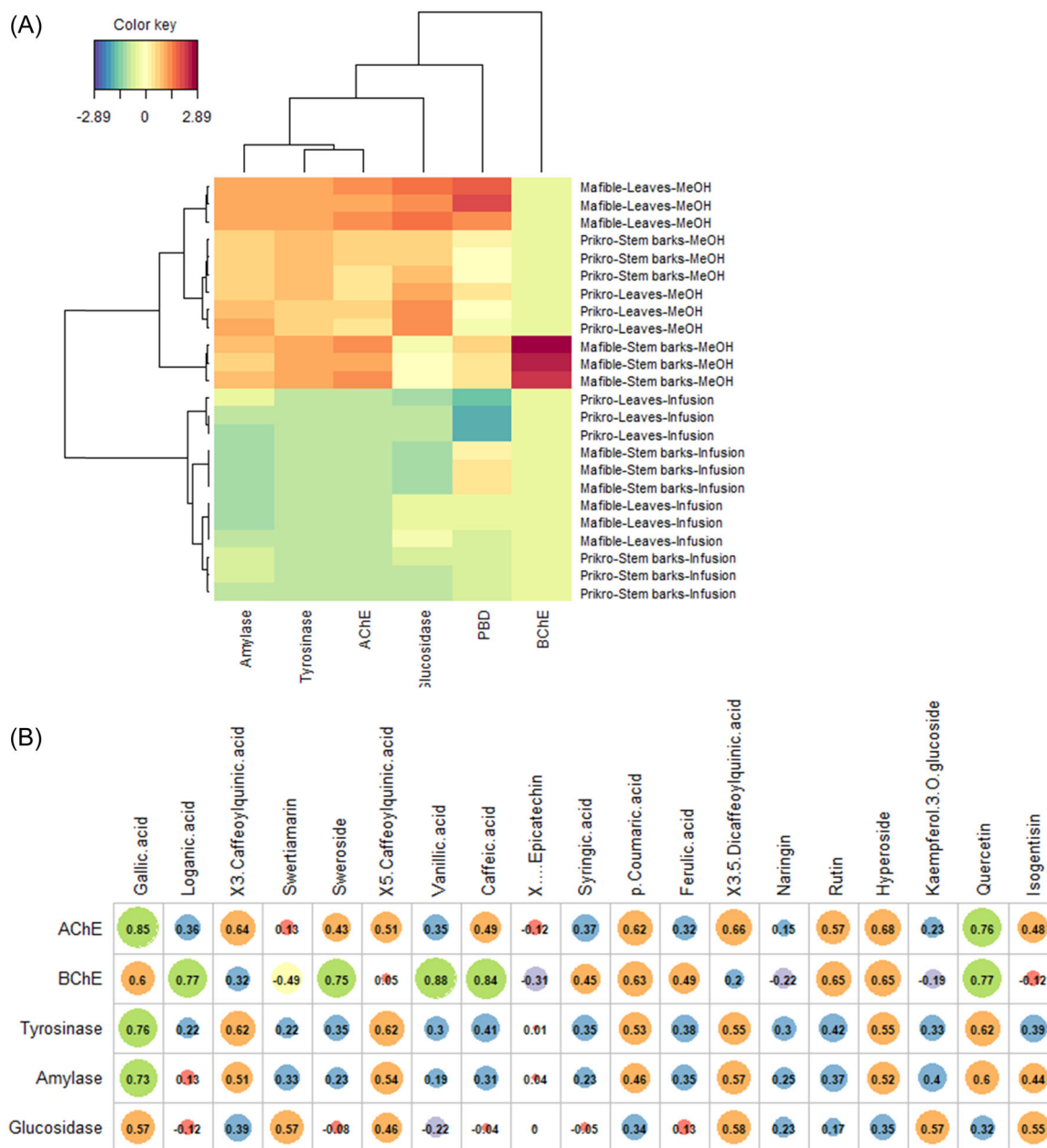


FIGURE 6 Clustered image map analysis (Red color: high activity and blue color: low activity) on enzyme inhibitory activity data set of *A. djalensis* extracts (A) and relationship between enzyme inhibitory activities and individual phytochemicals (B).

of molecular docking is to determine the correct ligand binding mode and to roughly estimate its binding propensity (Meng et al., 2011), which has been achieved in this study. Therefore, these compounds possibly exert their biological activities by binding to the active site of the studied enzymes.

4 | CONCLUSIONS

In this study, methanolic and infusion leaf and stem bark extracts of *A. djalensis* collected from two locations, were tested for their phytochemical contents, antioxidant

and enzyme inhibitory properties. In general, the stem bark extracts were found to yield richer total bioactive contents compared to the leaf extracts. Interestingly, the extracts of *A. djalensis* from Mafiblé were revealed to possess the highest total bioactive contents, especially the stem bark extracts compared to that from Prikro. Moreover, while all extracts displayed antioxidant potential, the leaf methanolic extract of *A. djalensis* from Mafiblé exhibited the most potent antioxidant activity, followed by the stem bark methanolic extract. Besides, extracts of *A. djalensis* from Mafiblé showed relatively better antioxidant activity compared to that from Prikro. As for the enzyme inhibition, while the

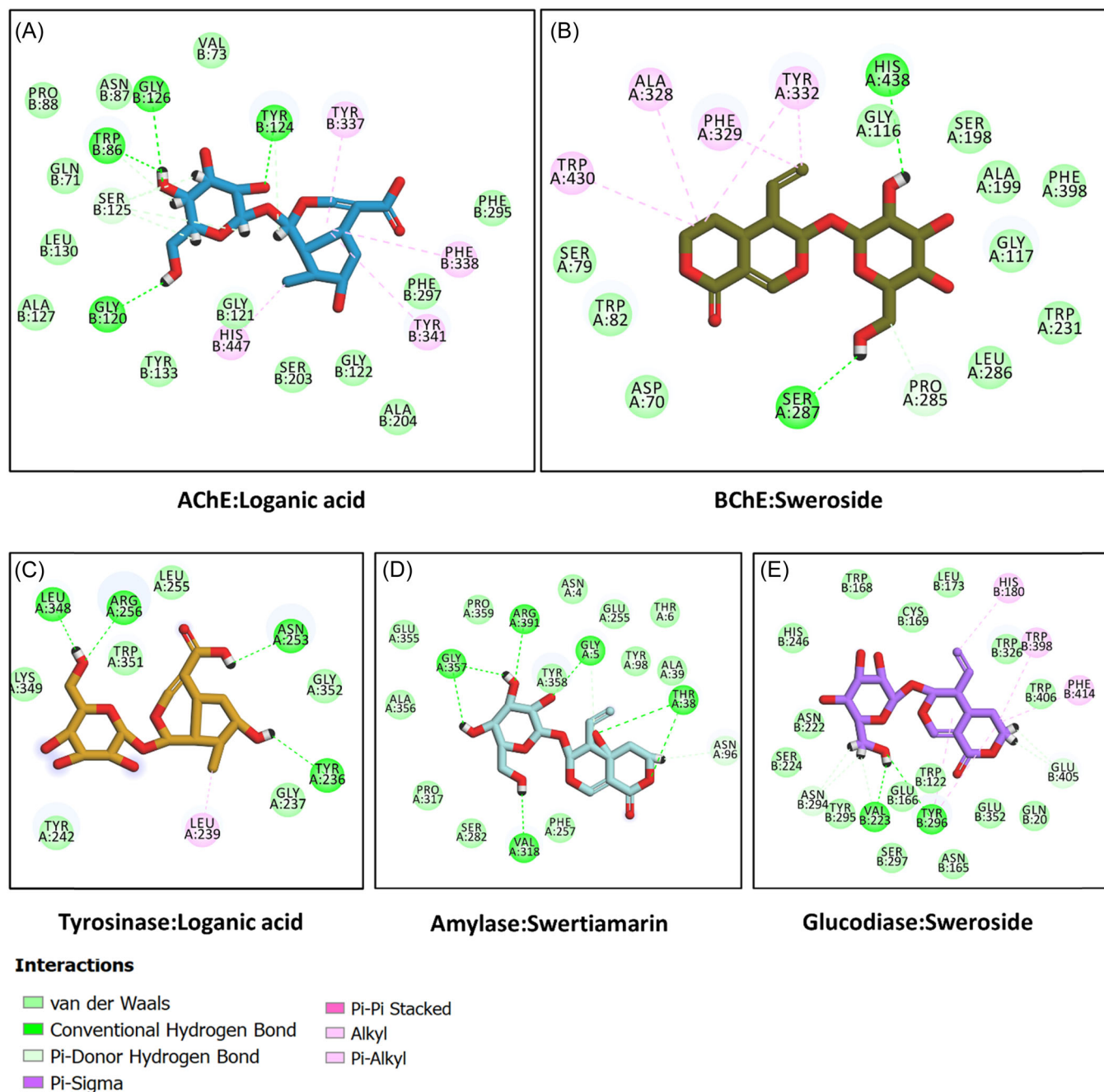


FIGURE 7 Protein–ligand interaction: (A) AChE and loganic acid, (B) BChE and sweroside (D), tyrosinase and loganic acid, (E) amylase and swertiamarin, and (F) glucosidase and sweroside.

infusion extracts were found to be inactive against the tested enzymes, or weak inhibitors, the other extracts exerted differential inhibitory properties. The methanolic extracts were mostly better inhibitors compared to the infusion extracts. Overall, the extracts of *A. djalensis* from Mafiblé showed better total phenolic and bioactive contents as well as antioxidant activity compared to Prikro extracts. Therefore, this study demonstrated some interesting results, for instance on the overall therapeutic potentials of this plant including the influence of

different locations on the chemical and biological profiles, and the plant part or even the solvent best suited for phytochemical extraction to maximize the use of this plant for medicinal purposes.

AUTHOR CONTRIBUTIONS

Kouadio Ibrahim Sinan: Conceptualization; Data curation; Software. **Gokhan Zengin:** Conceptualization; Data curation. **Abdullahi Ibrahim Uba:** Formal analysis; Investigation; Methodology. **Giovanni Caprioli:**

Investigation; Methodology; Validation. **Simone Angeloni**: Investigation; Methodology; Writing—original draft. **Sauro Vittori**: Funding acquisition; Investigation; Methodology; Writing—original draft. **Sharmeen Jugreet**: Investigation; Methodology; Writing—original draft. **Ouattara Katinan Etienne**: Investigation; Methodology. **Mohamad Ali Shariati**: Investigation; Methodology. **Mohamad Fawzi Mahomoodally**: Investigation; Methodology; Writing—original draft.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

None declared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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