BMC Complementary Medicine and Therapies

RESEARCH

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Secondary metabolic profiling, antioxidant potential, enzyme inhibitory activities and in silico and ADME studies: a multifunctional approach to reveal medicinal and industrial potential of *Tanacetum falconeri*

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Abstract

Tanacetum falconeri is a significant flowering plant that possesses cytotoxic, insecticidal, antibacterial, and phytotoxic properties. Its chemodiversity and bioactivities, however, have not been thoroughly investigated. In this work, several extracts from various parts of *T. falconeri* were assessed for their chemical profile, antioxidant activity, and potential for enzyme inhibition. The total phenolic contents of *T. falconeri* varied from 40.28 ± 0.47 mg GAE/g to 11.92 ± 0.22 mg GAE/g in various extracts, while flavonoid contents were found highest in TFFM (36.79 ± 0.36 mg QE/g extract) and lowest (11.08 ± 0.22 mg QE/g extract) in TFSC (chloroform extract of stem) in similar pattern as found in total phenolic contents. Highest DPPH inhibition was observed for TFFC (49.58 ± 0.11 mg TE/g extract) and TFSM (46.33 ± 0.10 mg TE/g extract), whereas, TFSM was also potentially active against (98.95 ± 0.57 mg TE/g) ABTS radical. In addition, TFSM was also most active in metal reducing assays: CUPRAC (151.76 ± 1.59 mg TE/g extract) and FRAP (101.30 ± 0.32 mg TE/g extract). In phosphomolybdenum assay, the highest activity was found for TFFE (1.71 ± 0.03 mg TE/g extract), TFSM (1.64 ± 0.035 mg TE/g extract), TFSH (1.60 ± 0.033 mg TE/g extract) and TFFH (1.58 ± 0.08 mg TE/g extract), while highest metal chelating activity was recorded for TFSH (25.93 ± 0.79 mg EDTAE/g extract), TFSE (22.90 ± 1.12 mg EDTAE/g extract) and TFSC (19.31 ± 0.50 mg EDTAE/g extract). In biological screening, all extracts had stronger inhibitory capacity against AChE while in case of BChE the chloroform extract of flower (TFFC) and stem (TFSC) showed the highest activities with inhibitory values of 2.57 ± 0.24 and 2.10 ± 0.18 respectively. Similarly, TFFC and TFSC had stronger inhibitory capacity (1.09 ± 0.015 and 1.08 ± 0.002 mmol ACAE/g extract) against α-Amylase and (0.50 ± 0.02 and 0.55 ± 0.02 mmol ACAE/g extract) α-Glucosidase. UHPLC-MS study of methanolic extract revealed the presence of 133 components including sterols, triterpenes, flavonoids, alkaloids, and coumarins. The total

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phenolic contents were substantially linked with all antioxidant assays in multivariate analysis. These findings were validated by docking investigations, which revealed that the selected compounds exhibited high binding free energy with the enzymes tested. Finally, it was found that *T. falconeri* is a viable industrial crop with potential use in the production of functional goods and nutraceuticals.

Keywords *Tanacetum falconeri*, Total bioactive contents; antioxidant activities, Enzyme inhibition activities, In silico studies

Introduction

Tanacetum falconeri is an important flowering herb belong to plant family Asteraceae [1]. It is mostly found in the rocky talus, near the lakes, valley plains or grassy ridges in different parts of Pakistan. Locally, the powdered leaves and extract of leaves of *T. falconeri* is used against various abdominal problems, whereas, its flowers and buds are beneficial in treating asthma, jaundice and blood pressure problems [2, 3]. Different plant parts are utilised to treat joint discomfort after being dried in the shade [4]. The habitants of Kallaway Indians and the Andes mountains used these plants for back ache, abdominal pain and gastric trouble [5]. The Mexican people used it as a tonic to regulate menstruation and as an antispasmodic. In Venezuela, it's used to cure earaches [6]. A scanty work on chemodiversity and biological potential of *T. falconeri* has been reported in literature, however, other *Tanacetum* plants are rich in terpenes mostly as essential oils [7–13], sterols [14–16], phenolic acids and flavonoids [17]. Due to the presence of variety of bioactive compounds, *Tanacetum* plants extracts have shown various biological activities like anti-inflammatory, antiviral, antifungal, antibacterial and antioxidant [18], edema [19], antibacterial [14, 20], fungicidal activity [21], antioxidant [22], anti-inflammatory [23], anthelmintic, Anticoagulant and antifibrinolytic, insecticidal [14], and anti-ulcer [24, 25] and antitumor [26]. *Tanacetum* plants have also showed anti-Leishmanial, antibacterial [27], antimalarial [28] activities. Despite of the lack of phytochemical investigation, *Tanacetum* plants has received recognition as a potential nematocidal, insecticidal, antibacterial, cytotoxic, and phytotoxic herbs [29]. Therefore, the diverse chemical profiling of *Tanacetum* plants, and their medicinal uses prompted us to investigate *T. falconeri* for its chemodiversity and biological potential. The goal of this study was to evaluate the traditional therapeutic applications of *T. falconeri* by evaluating the various extracts for their total bioactive content, full secondary metabolic profile, and bioactivities. In vitro tests were conducted to evaluate the anti-oxidant (DPPH, ABTS, FRAP, CUPRAC, phosphomolybdenum, ferrous chelating) and enzyme inhibitory capabilities of all extracts against various enzymes linked to skin, neurodegenerative, and diabetic illnesses. Additionally, multivariate analysis and docking investigations were carried out.

Experimental procedures

Collection of the plant material and identification

The plant material was collected from Shigar District, Gilgit-Baltistan, Pakistan and was identified by Dr. Zaheer Abbas, a taxonomist at the University of Education, DG Khan Campus, Dera Ghazi Khan, where a voucher specimen No. BT-0063 has been deposited in the herbarium of same university.

Preparation of the extracts

The collected plant material was divided into flower (TFF) and stem with leaves (TFS) parts, which were then dried under shade for one week. Each part (600 and 800 g, respectively) was divided into four parts, which were then extracted separately through maceration using *n*-hexane, chloroform, ethyl acetate and methanol to get crude extracts of the stem: TFSM: methanolic extract of stem; TFSH: hexane extract of stem; TFSE: ethyl acetate extract of stem; TFSC: chloroform extract of stem and flowers extracts: TFFM: methanolic extract of flowers; TFFH: hexane extract of flowers; TFFE: ethyl acetate extract of flowers; TFFC: chloroform extract of flowers. All these extracts were then studied for their phenolic and flavonoid contents, antioxidant and enzyme inhibition studies and chemodiversity.

Estimation of Total phenolic (TPC) and Total flavonoid (TFC) contents

The Estimation of total phenolic (TPC) and total flavonoid (TFC) contents were done through same methods as we reported previously [30–33]. The results of total phenolic contents (TPC) were presented in milligrams of gallic acid equivalent per grams of extract (mg GAE/g extract). The total flavonoid contents (TFC) results were reported in milligrams of rutin equivalent per grams of extract (mg RE/g extract).

Antioxidant activities assays

The antioxidant activities of extracts were measured by following pre-established protocols as we reported

previously [30–33]. For FRAP, ABTS, DPPH, CUPRAC, and total antioxidant capacity, trolox equivalent was utilized as standard and results were expressed as mg TE/g extract; while for metal chelating assays, ethylene diamine tetraacetic acid (EDTA) was the standard and results were expressed as mg TE/g extract.

Enzyme inhibition assays

The α-amylase, α-glucosidase, BChE, tyrosinase, and AChE enzyme inhibitory assays were conducted using previously published methods [30–33]. Acarbose (mmol ACAE/g extract) was used as a standard to measure the inhibitory activity of α-amylase and α-glucosidase. Galantamine (mg GALAE/g extract) was used to measure the inhibitory activity of AChE and BChE, and kojic acid (mmol KAE/g extract) was used to measure the inhibitory activity of tyrosinase.

UHPLC-MS analysis

UHPLC-MS (ultra-high performance liquid chromatography mass spectrometry) analysis was used to profile secondary metabolites using an Agilent 1290 Infinity UHPLC system coupled to an Agilent 6520 Accurate-Mass Q-TOF mass spectrometer with dual ESI source, as we previously reported [30–32]. The column was an Agilent Zorbax Eclipse XDB-C18 with 3.5 m in thickness and 2.1 × 150 mm in diameter. A 0.1% formic acid solution in water served as mobile phase A, while a 0.1% formic acid solution in acetonitrile served as mobile phase B. A consistent flow rate of 0.5 millilitres per minute was maintained. One microliter of methanolic extract was given for twenty-five minutes, and then there was a five-minute post-run period. The secondary metabolites were found using the METLIN database.

Statistical analysis

The experiments were performed in triplicate, and differences between the extracts were compared using an ANOVA and Tukey's test. Pearson correlation analysis was used to establish the link between total bioactive components and biological activity assays. Graph Pad Prism (version 9.2) was used for the analysis. To assess the degree of similarity or difference between the extracts, a PCA was carried out using SIMCA (version 14.0).

Docking study methodology

The chemical structures of the five enzymes with the highest resolution were downloaded from the protein data bank in PDB format. Discovery Studio (DS 2021Client) software was employed to formulate protein molecules. Attached chemical moieties (water molecules and other ligand) were removed from macromolecules. Afterward, they were transferred onto the PyRx program (version 0.8) for docking purposes in pdbqt file that contains a protein structure with hydrogens in all polar residues. The structures of selected ligands were acquired from the Pubchem as 3D SDF formats. The software specification and procedure of docking were followed as described by Ahmed et al., [34]. The enzyme molecules were loaded into PyRx and converted to macromolecules by using autodock embedded in PyRx software. Then the ligands were attached using the open babel tool, and energy was minimized to obtain the stable structure; then, ligands were converted to pdbqt format. The docking site on the protein target was defined by establishing a grid box, which was maximized using "maximize" option for better coverage of active site and exhaustiveness was 8. The other settings of the software were used as "default". The best conformation with the lowest docked energy was chosen after the docking search was completed. The molecular docking result for each compound was visualized as an output pdbqt file by using the molecular graphics laboratory (mgltool) tool. Interactions were finally visualized in discovery studio by using mgltool, to determine some specific contacts between the atoms of the test compounds and amino acids residues of the studied protein molecules [35].

Results and discussion

Total phenolic (TPC) and flavonoid (TFC) contents of T. falconeri

Phenolic compounds are important component of nutraceuticals and functional foods because of their antioxidant properties. The antioxidant properties of phenolics are usually attributed to the presence of hydroxyl group(s) on the benzene ring, which goes about an electron donor and consequently and straight forwardly includes in quenching free radicals. In the present study, several solvent-based crude stem and flower extracts of *T. falconeri* were screened for their total phenolic and flavonoid contents. Total phenolic contents (TPC) observed in the methanol extract of flower (TFFM) were high (40.28 ± 0.47 mg GAE/g extract), followed by the TFFH extract (33.00 ± 0.67 mg GAE/g extract). Although the same trend of TPC for stem extracts was seen in TFSM (22.21 ± 0.17 mg GAE/g extract) and TFSH (24.34 ± 0.49 mg GAE/g extract) but were lower than those of respective extracts of the flower. Ethyl acetate extracts from both the sources were next in line (Table 1). Similarly, total flavonoids contents (TFC) were also observed high in flower extracts (TFFM 36.79 ± 0.36 mg QE/g extract and TFFH 32.80 ± 0.80 mg QE/g extract), followed by stem extracts (TFSM 17.68 ± 0.32 mg QE/g extract and TFSE 23.38 ± 0.17 mg QE/g extract). In both the cases,

Table 1 Total bioactive contents of *T. falconeri*

Test Samples	TPC (mg GAE/g extract)	TFC (mg QE/g extract)
TFFM	40.28 ± 0.47^{a}	36.79 ± 0.36^{a}
TFFH	33.00 ± 0.67^{b}	32.80 ± 0.80^{b}
TFFE	17.37 ± 0.23^{e}	11.65 ± 0.09^{f}
TFFC	11.92 ± 0.22^{f}	3.22 ± 0.05^{g}
TFSM	22.21 ± 0.17^{d}	17.68 ± 0.32^{d}
TFSH	24.34 ± 0.49^{c}	13.39 ± 0.30^{e}
TFSE	22.18 ± 0.33^{d}	23.38 ± 0.17^{c}
TFSC	18.07 ± 0.18^{e}	11.08 ± 0.22^{f}

TFFM: methanolic extract of flower of *T. falconeri*; TFFH: hexane extract of flower of *T. falconeri*; TFFE: ethyl acetate extract of flower of *T. falconeri*; TFFC: chloroform extract of flower of *T. falconeri*; TFSM: methanolic extract of stem of *T. falconeri*; TFSH: hexane extract of stem of *T. falconeri*; TFSE: ethyl acetate extract of stem of *T. falconeri*; TFSC: chloroform extract of stem of *T. falconeri*. Different letters in same column indicate significant differences in the tested extracts ($p < 0.05$)

lowest phenolic and flavonoid contents were calculated in chloroform extracts (Table 1). Usually phenolics and flavonoids are relatively polar compounds; therefore, their high concentration in methanolic or ethyl acetate extracts seems reasonable, however, in case of flower extracts (TFFH and TFSH), the high amount of phenolic contents could be attributed to the possible presence of esters of phenolic acids in the extracts. Literature reports also substantiate our findings where methanolic extracts of *Tanacetum* plants have been reported to be rich in phenolic contents [36]. Another report describes that *Tanacetum* species produce high level of vanillic acid, and caffeic acid, catechin and quercetin [37] and other phenolics and flavonoids [38, 39].; The presence of caffeoylquinic acids in *Tanacetum* species [40, 41] substantiates our deduction that phenolic acid esters are present in *T. falconeri*, which are extracted in low polar solvents, and thus TFFH and TFSH also afforded high amount of phenolic contents.

Antioxidant activities of the extracts of T. falconeri

Research showed that the antioxidant activity of a plant extract is usually associated to the phenolic contents, i.e. higher the phenolic contents, higher will be the activity [42]. However, in the present study, the highest DPPH free radical scavenging activity (TFFM; 49.58 ± 0.11 mg TE/g extract) was associated to the methanolic flower extract, which is followed by *n*-hexane flower extract (TFFH; 47.91 ± 0.17 mg TE/g extract), whereas, methanolic stem extract (TFSM) also showed nearly similar inhibition (43.75 ± 0.41 mg TE/g extract). It is already predicted that the presence of phenolic contents in low polar solvents could be of the nature of phenolic acid esters. Literature search revealed that phenolic acid esters are potent antioxidants [43], therefore, the activity of TFFM could be attributed to such kind of compounds and other metabolites. On the other hand, the higher DPPH free radical inhibitory potential of TFSM could be attested for its high phenolic contents (Table 2). TFSM and TFFH were also significantly active, while other extracts were found inactive (Table 2). In case of ABTS free radical activity same pattern was observed as in DPPH and TFFM exhibited highest inhibition value (112.61 ± 0.15 mg TE/g extract). The next in line were TFFH, TFSM and TFSE (Table 2) with values of 84.60 ± 0.57, 73.43 ± 2.77 and 62.51 ± 0.97 respectively. In metal ion reducing power assays, again the TFFM was highly active (CUPRAC: 160.48 ± 6.59 mg TE/g extract; FRAP: 102.58 ± 2.62 mg TE/g extract), followed by the methanolic extract of stem (TFSM). All other extracts also exhibited significant and comparable metal reducing power (Table 2). TFSE was most active in phosphomolybdenum with the value of 1.71 ± 0.03 mg TE/g extract, whereas, TFFH and TFSH were also significantly active with the values of 1.64 ± 0.00 and 1.58 ± 0.08 mg TE/g extract,

Table 2 Antioxidant activities of the extracts of *T. falconeri*

Test Samples	DPPH (mg TE/g extract)	ABTS (mg TE/g extract)	CUPRAC (mg TE/g extract)	FRAP (mg TE/g extract)	Phosphomolybdenum (mg TE/g extract)	metal chelating (mg EDTAE/g extract)
TFFM	49.58 ± 0.11^{a}	112.61 ± 0.15^{a}	160.48 ± 6.59^{a}	102.58 ± 2.62^{a}	1.12 ± 0.01^{cd}	13.02 ± 0.39^{c}
TFFH	47.91 ± 0.17^{b}	84.60 ± 0.57^{b}	123.27 ± 2.38^{b}	67.17 ± 0.21^{b}	1.64 ± 0.00^{a}	10.05 ± 0.60^{d}
TFFE	5.87 ± 0.45^{f}	36.60 ± 1.15^{f}	49.58 ± 2.90^{d}	17.93 ± 0.05^{f}	1.25 ± 0.02^{bc}	8.73 ± 0.29^{d}
TFFC	Not active	15.95 ± 1.20^{g}	35.17 ± 0.94^{e}	15.23 ± 0.48^{f}	1.00 ± 0.02^{d}	14.03 ± 0.28^{bc}
TFSM	43.75 ± 0.41^{c}	73.43 ± 2.77^{c}	82.73 ± 1.59^{c}	50.64 ± 0.22^{c}	1.10 ± 0.02^{d}	15.57 ± 0.22^{b}
TFSH	19.20 ± 0.37^{e}	47.23 ± 1.11^{e}	77.22 ± 1.98^{c}	40.40 ± 1.36^{d}	1.58 ± 0.08^{a}	9.31 ± 0.70^{d}
TFSE	22.42 ± 0.38^{d}	62.51 ± 0.97^{d}	77.13 ± 0.88^{c}	50.20 ± 0.82^{c}	1.71 ± 0.03^{a}	9.04 ± 0.69^{d}
TFSC	5.95 ± 0.61^{f}	38.33 ± 2.11^{f}	51.75 ± 0.52^{d}	23.93 ± 0.13^{e}	1.36 ± 0.03^{b}	18.06 ± 0.61^{a}

TFFM: methanolic extract of flower of *T. falconeri*; TFFH: hexane extract of flower of *T. falconeri*; TFFE: ethyl acetate extract of flower of *T. falconeri*; TFFC: chloroform extract of flower of *T. falconeri*; TFSM: methanolic extract of stem of *T. falconeri*; TFSH: hexane extract of stem of *T. falconeri*; TFSE: ethyl acetate extract of stem of *T. falconeri*; TFSC: methanolic extract of stem of *T. falconeri*. Different letters in same column indicate significant differences in the tested extracts ($p < 0.05$)

respectively. Highest metal chelating activity was found for stem extracts, since TFSC and TFSM displayed chelating power as 18.06 ± 0.61 and 15.57 ± 0.22 mg TE/g extract, whereas, flower extracts were found weak chelators (Table 2). It if further noticed that more polar extracts were also weak chelators, however, overall the present study revealed that *T. falconeri* is a potential antioxidant plant to be considered for its uses in health promoting formulations.

Enzyme inhibition activities of the extracts of T. falconeri

AChE and BChE enzyme inhibition activities

Alzheimer's disease (AD), a noncommunicable disease (NCDs) has been identified as a largely increasing health challenge worldwide. It is an irreversible, progressive form of dementia, associated with an ongoing decline of brain functioning [44] and thus causes memory loss. The World Health Organization (WHO) has reported that more than 30 million people are afflicted by AD and this number is expected to become double every two decades to reach ~ 115 million by 2050. This problem is thus expected to weaken the social and economic development and may affect the social services [45]. Acetylcholine (ACh) and buytrylcholine (BCh) are important neurotransmitters requires for proper brain, memory and body functioning Therefore, low levels of cholines lead to memory issues and muscle disorders. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are the enzymes that hydrolyse acetycholine and butyrylcholine, respectively [46]. The inhibitors of these two enzymes results into accumulation of the neurotransmitter acetylcholine and enhanced stimulation of postsynaptic cholinergic receptors [47, 48]. Natural products have already proven to be promising sources of useful acetylcholinesterase (AChE) inhibitors [49]. The currently approved drugs for AD, galantamine and rivastigmine, are plant-derived alkaloids, which offer symptomatic relief from AD [50]. These facts suggest to investigate the use of medicinal plants and their formulations to prevent and treat neurodegenerative disease [51].

In this study, all the extracts of *T. falconeri* were evaluated against AChE and BChE enzymes. Methanolic (TFFM) and ethyl acetate (TFFE) extracts f flowers, while ethyl acetate (TFSE) and chloroform (TFSC) extracts of stem were most but equally active with inhibitory values as 4.09 ± 0.09, 4.53 ± 0.13, 4.00 ± 0.23 and 4.03 ± 0.22 mg GALAE/g extract, respectively, against AChE, whereas, TFFE, TFFC and TFSC were most active against BChE with values as 2.09 ± 0.18, 2.57 ± 0.24 and 2.10 ± 0.18 mg GALAE/g extract. These observations revealed that ethyl acetate and chloroform extracts are more active against these enzymes.

Tyrosinase enzyme inhibition activities

Browning of raw food and hyperpigmentation of human skin are two undesirable processes caused a group of copper-containing enzyme tyrosinase (EC 1.14. 18.1). Hyper activity of tyrosinase causes results in a less attractive appearance and loss in nutritional quality of food and blackening of human skin [52]. Further, over production of melanin in human skin causes several skin disorders such as melasma, senile lentigines and freckles and thus exert a considerable psychosomatic effect on affected patients [53]. These problems can be controlled by using tyrosinase inhibitors. Presently available tyrosinase inhibitors like hydroquinone, arbutin, kojic acid, ascorbic acid, ellagic acid and others have different problems either in their use or the bioavailability [54].Therefore, there is a great need to discover and develop new but safer tyrosinase inhibitors. For his purpose, the medicinal plant extracts are the main agents being researched and used as tyrosinase inhibitors in these days. In the present work various extracts of T. falconeri were evaluated for their tyrosinase inhibitory activity. Methanolic extracts of both flowers (TFFM) and stem TFSM) of *T. falconeri* were the most active with inhibition values as 35.53 ± 0.35 and 35.30 ± 0.70 mg KAE/g extract, respectively followed by the hexane extracts (29.96 ± 0.10 and 32.41 ± 1.91 mg KAE/g extract, respectively. All other extracts exhibited equal but significant inhibitory potential (Table 3), which disclosed that *T. falconeri* can be a potential ingredient in cosmetic and food industry.

α-Amylase and α-glucosidase enzyme inhibition activities

Diabetes mellitus is another major non-communicable metabolic disease that has high impact on health and economy. A published report revealed that only in 2014, 4.9 million deaths were recorded due to diabetes [55]. In diabetic patients usually the blood glucose level increases after taking meal and thus causes postprandial hyperglycemia [56]. The glycosidic linkage in carbohydrates is broken by α-amylase to produce oligosaccharides, which are then degraded to glucose by α-glucosidase [57]. Since both the enzymes digest the carbohydrates and cause diabetes [55]; inhibition of the activity of these enzymes can delay the increase in blood glucose level and reduce the risk of developing diabetes [58]. Among current inhibitors, only acarbose inhibits both α-amylase and α-glucosidase, whereas, miglitol and voglibose inhibit only α-glucosidase [59, 60]. Literature search revealed that some of the plant extracts or pure phytochemicals were found effective against both enzymes [61–64], which leads to conclude that medicinal plants can serve as potential antidiabetic agents. Therefore, in the present study, the flower and stem extracts of *T. falconeri* were

Table 3 Enzyme inhibition activities of the extracts of *T. falconeri*

Test Samples	AChE (mg GALAE/g extract)	BChE (mg GALAE/g extract)	Tyrosinase (mg KAE/g extract)	α-Amylase (mg ACAE/g extract)	α-Glucosidase (mg ACAE/g extract)
TFFM	4.09 ± 0.09^{ab}	0.47 ± 0.08^{cd}	35.53 ± 0.35^{a}	0.38 ± 0.009^{c}	0.46 ± 0.002^{d}
TFFH	3.40 ± 0.28^{cd}	0.38 ± 0.06^{d}	29.96 ± 0.10^{bc}	0.48 ± 0.02^{b}	0.86 ± 0.001^{c}
TFFE	4.53 ± 0.13^{a}	2.09 ± 0.18^{a}	27.00 ± 0.90^{c}	0.55 ± 0.02^{ab}	1.06 ± 0.002^{a}
TFFC	4.14 ± 0.08^{ab}	2.57 ± 0.24^{a}	27.25 ± 1.29^{c}	0.50 ± 0.02^{ab}	1.09 ± 0.015^{a}
TFSM	3.24 ± 0.12^{d}	0.94 ± 0.09^{bc}	35.30 ± 0.70^{a}	0.41 ± 0.01^{c}	0.91 ± 0.003^{bc}
TFSH	3.67 ± 0.12^{bcd}	1.46 ± 0.10^{b}	$32.4\,1 \pm 1.91^{ab}$	0.53 ± 0.01^{ab}	0.87 ± 0.015^{c}
TFSE	4.00 ± 0.23^{abc}	1.16 ± 0.17^{b}	26.79 ± 0.63^{c}	0.53 ± 0.01^{ab}	1.02 ± 0.107^{ab}
TFSC	4.03 ± 0.22^{ab}	2.10 ± 0.18^{a}	27.50 ± 1.50^{c}	0.55 ± 0.02^{a}	1.08 ± 0.002^{a}

TFFM: methanolic extract of flower of *T. falconeri*; TFFH: hexane extract of flower of *T. falconeri*; TFFE: ethyl acetate extract of flower of *T. falconeri*; TFFC: chloroform extract of flower of *T. falconeri*; TFSM: methanolic extract of stem of *T. falconeri*; TFSH: hexane extract of stem of *T. falconeri*; TFSE: ethyl acetate extract of stem of *T. falconeri*; TFSC: methanolic extract of stem of *T. falconeri*. Different letters in same column indicate significant differences in the tested extracts ($p < 0.05$)

evaluated for their inhibitory potential against α-amylase and α-glucosidase. Against amylase, all the extracts exhibited significant activity with inhibitory values in the range of 0.38 ± 0.009 to 0.55 ± 0.002 mg ACAE/g extract, while against α-glucosidase the inhibitory values were observed between 0.46 ± 0.002 to 1.09 ± 0.015 mg ACAE/g extract, with lowest potential in both the cases was observed for methanolic extracts (Table 3). It is reported that the plant extracts exhibit antidiabetic properties due to the combined effect of biologically active compounds like polyphenols, carotenoids, lignans, coumarins, glucosinolates, etc. [65]. These plant metabolites as a combined effect, improve the performance of pancreatic tissue by increasing insulin secretions or by reducing the intestinal absorption of glucose [66]. Therefore, the anti-amylase and anti-glucosidase activities of the extracts of *T. falconeri* could be attributed to the presence of such metabolites. Literature reports revealed that most of the plant extracts and pure compounds exhibit selective inhibition against either α-amylase or α-glucosidase; while only fewer have been found active against both the enzymes [55]. Overall the crude extracts of *T. falconeri* were found significantly active against both the enzymes; therefore, it can be a potential component of crude antidiabetic drugs.

UHPLC-MS Analysis

UHPLC-MS Analysis of methanolic extract (Fig. 1) of flowers result in identification of 133 compounds (Table 4) of various secondary metabolites class mainly phenolic, flavonoids, Alkaloids, terpenoids and steroids. The presence of important phenolic and flavonoids compounds like 6-Caffeoylsucrose, 3-O-Feruloylquinic acid, Brosimacutin C, Quinic acid, Rutacultin, Castamollissin, Kaempferol 3-p-coumarate and Methylsyringin may be responsible for antioxidant activities [67]. These results demonstrated that *T. falconeri* is not limited to a specific class of secondary metabolites and can create a broad variety of compounds. Chemodiversity makes *T. falconeri* a valuable herb with a broad range of bioactivities.

Data analysis

Multivariate analysis provides a bridge between diverse parameters and their interactions. This makes it a fundamental tool in phytochemical studies to gain more information on the relationship between the chemical

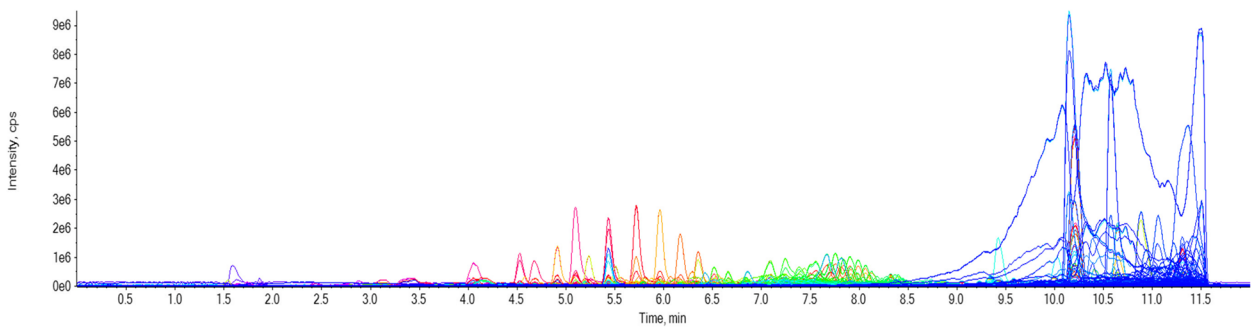

Fig. 1 Total ion chromatogram of UHPLC-MS of methnolic extract of *T. falconeri*

Table 4 UHPLC-MS analysis of methanolic extract of flower of *T. falconeri*

Sr. No	Analyte Peak Name	Retention Time	Area / Height	Molecular formula	Compound name	Mass	Class of compound
1	381.0730 (M + K^+)	1.51	3.93	$C_{19}H_{18}O_6$	1,5,8-Trihydroxy-3-methyl-$_2$-prenylxanthone	342.3	Xanthone
2	317.0928	1.48	4.01	$C_{13}H_{16}O_9$	Ginnalin B	316.0794	Phenolic acid
3	429.2146	1.49	4.97	$C_{23}H_{28}N_2O_6$	Carapanaubine	428.1947	Indolizine
4	319.0642	1.50	4.77	$C_{18}H_{10}N_2O_4$	Prekinamycin	318.0641	Alkaloids
5	439.1663	1.51	3.80	$C_{21}H_{26}O_{10}$	sec-o-Glucosylhamaudol	438.1526	Chromene
6	321.0363	1.50	3.45	$C_{18}H_8O_6$	Erosnin	320.0321	Coumestan
7	295.0925	1.56	3.65	$C_{18}H_{14}O_4$	7-Acetyloxy-2-methylisoflavone	294.0892	Isoflavone
8	367.1182	1.66	3.96	$C_{21}H_{18}O_6$	Isoglycyrol	366.1103	Phyto
9	353.0613	1.70	3.64	$C_{19}H_{12}O_7$	Daphnoretin	352.0583	Coumarin
10	685.2285	1.73	4.65	$C_{37}H_{36}N_2O_{11}$	Citbismine C	684.2319	Acridine
11	684.2245 (M + $NH4^+$)	1.73	4.39	$C_{30}H_{34}O_{17}$	Peonidin acetyl 3,5-diglucoside	666.1796	Anthocyanidine glycoside
12	505.1489	1.74	4.67	$C_{21}H_{28}O_{14}$	6-Caffeoylsucrose	504.1479	Cinnamic acid glycoside
13	244.0595	1.77	3.26	$C_{13}H_9NO_4$	Maculine	243.0532	Phyto
14	458.1606	1.81	4.17	$C_{20}H_{27}NO_{11}$	Amygdalin	457.1584	Cyanogen glycoside
15	367.0863	1.82	5.49	$C_{20}H_{14}O_7$	12a-Methoxydolineone	366.0740	Rotenoid flavonoid
16	306.1160	2.32	6.76	$C_{19}H_{15}NO_3$	N-Acetyldehydroanonaine	305.1052	Isoquinoline alkaloid
17	431.1402	2.45	4.00	$C_{22}H_{22}O_9$	Catechin 3-O-(1,6-dihydroxy-2-cyclohexene-1-carboxylate)	430.1264	Flavonoid
18	419.1085	2.49	2.96	$C_{20}H_{18}O_{10}$	Kaempferol 3-xyloside	418.0900	Falvonoid
19	312.1150	2.75	8.56	$C_{14}H_{17}NO_7$	Zierin	311.1005	Cyanogen glycoside
20	345.1150	3.03	7.13	$C_{22}H_{16}O_4$	Sanaganone	344.1049	Extended flavonoid
21	378.1217 (M + Na^+)	3.14	8.18	$C_{20}H_{21}NO_5$	Promucosine	355.1420	Alkaloid
22	307.1367	3.57	3.03	$C_{20}H_{18}O_3$	Lonchocarpin	306.1256	Chalcone
23	203.0709	3.70	13.48	$C_{12}H_{10}O_3$	5-Hydroxy-2,3-dimethyl-1,4-naphthoquinone	202.0630	Naphthaquinone
24	397.1801	3.66	5.28	$C_{20}H_{28}O_8$	4,5-Dihydroniveusin A	396.1784	Germacranolide
25	305.0988	3.76	9.90	$C_{16}H_{16}O_6$	4′-O-Methylcatechin	304.0947	Catechin
26	329.0808	3.87	5.95	$C_{14}H_{16}O_9$	BERGENIN	328.0794	Trihydroxybenzoic acid derivative
27	270.0759	3.87	5.71	$C_{15}H_{11}NO_4$	Evoxanthidine	269.0688	Acridine
28	319.1141 (M + Na^+)	4.06	8.67	$C_{17}H_{18}O_6$	Bryaflavan	318.1103	Isoflavane
29	279.1226	4.06	7.83	$C_{15}H_{18}O_5$	Artecanin	278.1154	Sesquiterpene lactone
30	372.1787 (M + $NH4^+$)	4.36	8.11	$C_{21}H_{22}O_5$	Mundulea flavanone B	354.1467	Flavanone
31	303.0833	4.26	7.97	$C_{16}H_{14}O_6$	Alysifolinone	302.0790	Flavanone
32	293.1148	4.38	6.39	$C_{19}H_{16}O_3$	Purpuritenin A	292.1099	Chalcone
33	325.1269 (M + CH3OH + H^+)	4.37	9.25	$C_{15}H_{16}O_6$	Dihydromikanolide	292.0947	Lactone
34	372.1803 (M + $NH4^+$)	4.36	7.46	$C_{21}H_{22}O_5$	Flemistrictin D	354.1467	Chalcone
35	369.1127	4.54	7.78	$C_{17}H_{20}O_9$	3-O-Feruloylquinic acid	368.1107	Quinic acid derivative
36	360.1805 (M + CH3OH + H^+)	4.54	5.57	$C_{19}H_{21}NO_4$	Norcorydine	327.1471	Alkaloid
37	323.1477	4.52	6.18	$C_{17}H_{22}O_6$	Tetraneurin A	322.1416	Sesquiterpene lactone
38	360.1891 (M + $NH4^+$)	4.53	4.99	$C_{20}H_{22}O_5$	Brosimacutin C	342.1467	Flavanone

Table 4 (continued)

Sr. No	Analyte Peak Name	Retention Time	Area / Height	Molecular formula	Compound name	Mass	Class of compound
39	239.1290	4.68	6.88	$C_{13}H_{18}O_4$	1-(3-Ethyl-2,4-dihydroxy-6-methoxyphenyl)-1-butanone	238.1205	Aromatic ketone
40	416.1874 (M + NH4$^+$)	4.75	6.14	$C_{19}H_{26}O_9$	Methyl 3,4-dihydroxy-5-prenylbenzoate 3-glucoside	398.1577	Tannin
41	369.1516	4.84	6.55	$C_{18}H_{24}O_8$	4-Hydroxy-3-prenylbenzoic acid glucoside	368.1471	Phenolic glycoside
42	281.1386	4.83	5.90	$C_{15}H_{20}O_5$	8-Deoxy-11,13-dihydroxygrosheimin	280.1311	Sesquiterpene lactone
43	332.1685 (M + NH_4^+)	4.83	5.55	$C_{18}H_{20}NO_4$	Litcubinine	314.1392	Alkaloids
44	279.1227	4.88	5.27	$C_{15}H_{18}O_5$	Artecanin (Tanacetum parthenium)	278.1154	Sesquiterpene lactone
45	191.0735	4.89	5.74	$C_{11}H_{10}O_3$	7-Hydroxy-2,5-dimethyl-4H-1-benzopyran-4-one	190.0630	Coumarin
46	332.1687	4.83	5.56	$C_{22}H_{21}NO_2$	Melochinone	331.1572	Quinoline
47	444.1823	5.04	9.40	$C_{23}H_{29}N_3O_2S_2$	Thiothixene	443.1701	Thioxanthene
48	404.2139 (M + CH3OH + H^+)	4.91	5.32	$C_{21}H_{25}NO_5$	Capaurine	371.1733	Alkaloid
49	549.2671	5.05	4.12	$C_{29}H_{40}O_{10}$	Archangelolide	548.2621	Sesquiterpene lactone
50	533.2355	5.03	4.87	$C_{28}H_{36}O_{10}$	Nomilinic acid	532.2308	Steroidal lactone
51	382.1971	5.05	4.80	$C_{19}H_{27}NO_7$	Petasitenine	381.1788	Spiro epoxide
52	285.1748	5.10	5.18	$C_{18}H_{22}NO_2$	6,7-Dihydro-4-(hydroxymethyl)-2-(p-hydroxyphenethyl)-7-methyl-5H-2-pyrindinium	284.1651	Phenol
53	283.1690	5.10	6.42	$C_{19}H_{22}O_2$	Miltirone	282.1620	Diterpenoid
54	461.2160	5.08	6.37	$C_{25}H_{32}O_8$	Aspidin	460.2097	Phloroglucinol
55	285.1595 (M + NH_4^+)	5.10	5.38	$C_{17}H_{17}NO_2$	Assoanine	267.1259	Phenanthridine
56	251.1291	5.14	5.79	$C_{14}H_{18}O_4$	Helinorbisabone	250.1205	Terpenoids
57	285.1329	5.14	5.55	$C_{14}H_{20}O_6$	2-Phenylethyl beta-D-glucopyranoside	284.1260	Glycoside
58	193.0680	5.21	3.75	$C_7H_{12}O_6$	Quinic acid	192.0634	Cyclitol carboxylic acid
59	452.2076	5.28	7.11	$C_{26}H_{29}NO_6$	Piscerythramine	451.1995	Flavonoids
60	335.1238	5.36	4.55	$C_{21}H_{18}O_4$	Calopogoniumisoflavone A	334.1205	Flavonoids
61	404.2241 (M + NH_4^+)	5.33	5.30	$C_{19}H_{30}O_8$	Citroside A	386.1941	Glycoside
62	331.1079	5.38	5.34	$C_{18}H_{18}O_6$	7-Hydroxy-5,8,2′-trimethoxyflavanone	330.1103	Flavonoids
63	267.1232	5.37	4.96	$C_{14}H_{18}O_5$	Sapidolide A	266.1154	Lactone
64	317.0991 (M + CH3OH + H^+)	5.37	10.44	$C_{16}H_{12}O_5$	6-Methylapigenin	284.0685	Flavonoids
65	346.2001 (M + NH_4^+)	5.48	7.36	$C_{20}H_{24}O_4$	Sclareapinone	328.1675	Quinone
66	411.1374	5.52	4.10	$C_{23}H_{22}O_7$	Pongapinone A	410.1366	Coumarin
67	367.1725	5.55	4.93	$C_{19}H_{26}O_7$	Orizabin	366.1679	Terpenoids
68	575.1614	5.46	1.36	$C_{35}H_{26}O_8$	Viniferal	574.1628	Benzofuran
69	323.1089	5.67	5.72	$C_{19}H_{16}NO_4$	Berberrubine	322.1079	Alkaloids
70	372.1986 (M + NH_4^+)	5.68	9.08	$C_{23}H_{27}NO_2$	Murrayazolinine	349.2042	Alkaloids
71	374.1769 (M + NH_4^+)	5.75	9.07	$C_{13}H_{24}O_{11}$	Galactopinitol A	356.1319	Glycoside
72	519.2568	5.74	9.43	$C_{24}H_{38}O_{12}$	Cinnamoside	518.2363	Phenolic amide
73	535.2872	5.75	4.63	$C_{29}H_{42}O_9$	Corchoroside A	534.2829	Cardenolide glycoside

Table 4 (continued)

Sr. No	Analyte Peak Name	Retention Time	Area / Height	Molecular formula	Compound name	Mass	Class of compound
74	418.2217 (M + CH3OH + H^+)	5.87	7.80	$C_{22}H_{27}NO_5$	O-Methylandrocymbine	385.1889	Alkaloids
75	335.1238	5.83	5.35	$C_{16}H_{18}N_2O_6$	Cappariloside A	334.1165	Indoles
76	561.1657	5.85	7.37	$C_{27}H_{28}O_{13}$	3′-Deoxymaysin	560.1530	Flavonoids
77	408.2128	5.97	5.41	$C_{25}H_{29}NO_4$	Ancistrocladine	407.2097	Nephthalenes
78	275.1255	5.89	9.18	$C_{16}H_{18}O_4$	Rutacultin	274.1205	Coumarin
79	282.1697 (M + NH_4^+)	5.89	5.37	$C_{15}H_{20}O_4$	Sequiterpene Lactone 326	264.1362	Terpenoids
80	353.1920	5.91	3.92	$C_{21}H_{24}N_2O_3$	Vobasine	352.1787	Alkaloids
81	563.1818	5.99	10.84	$C_{27}H_{30}O_{13}$	Rhamnellaflavoside A	562.1686	Flavanoid
82	369.1882	5.93	4.82	$C_{21}H_{24}N_2O_4$	Baloxine	368.1736	Alkaloid ester
83	469.1053	6.12	2.62	$C_{20}H_{20}O_{13}$	Castamollissin	468.0904	Phenolic
84	439.2165	6.10	4.62	$C_{26}H_{30}O_6$	Kanzonol G	438.2042	Flavonoids
85	318.0725	6.11	4.48	$C_{19}H_{11}NO_4$	Lettowianthine	317.0688	Alkaloids
86	606.3224	6.16	5.56	$C_{33}H_{43}N_5O_6$	Amphibine H	605.3213	Peptide
87	368.1673	6.16	6.28	$C_{18}H_{25}NO_7$	Isatidine	367.1631	Alkaloids
88	342.1887 (M + NH_4^+)	6.35	6.34	$C_{17}H_{24}O_6$	Chamissonolide	324.1573	Terpenoids
89	293.0782	6.19	4.71	$C_{18}H_{12}O_4$	Karanjin	292.0736	Flavonoids
90	507.3096	6.30	4.33	$C_{29}H_{38}N_4O_4$	Mucronine A	506.2893	Peptide
91	293.1751	6.42	4.04	$C_{17}H_{24}O_4$	9-Acetoxyfukinanolide	292.1675	Terpenoids
92	365.1555 (M + CH3OH + H^+)	6.45	13.62	$C_{18}H_{20}O_6$	3,3′-Dihydroxy-4′,5,7-trimethoxyflavan	332.1260	Flavonoids
93	375.1748 (M + Na^+)	6.45	7.96	$C_{21}H_{24}N_2O_3$	Ajmalicine	352.1787	Alkaloid
94	551.2326	6.51	3.47	$C_{31}H_{34}O_9$	Lappaol B	550.2203	Phenylpropanoids
95	369.2056	6.60	10.05	$C_{23}H_{28}O_4$	Quercetol B	368.1988	Phenylpropanoids
96	365.1331 (M + K^+)	6.64	9.65	$C_{19}H_{22}N_2O_3$	Alkaloid AQC2	326.1630	Alkaloids
97	369.1878	6.59	8.25	$C_{21}H_{24}N_2O_4$	Uncarine A	368.1736	Alkaloids
98	315.1191	6.67	5.06	$C_{18}H_{18}O_5$	Matteucinol	314.1154	Flavonoids
99	597.2793 (M + Na^+)	6.69	5.96	$C_{31}H_{42}O_{10}$	Asclepin	574.2778	Cardenolide glycoside
100	405.1265 (M + K^+)	6.65	5.97	$C_{21}H_{22}N_2O_4$	Apodine	366.1580	Alkaloids
101	402.2446 (M + NH_4^+)	6.75	9.74	$C_{20}H_{32}O_7$	Cinnzeylanol	384.2148	Terpenoids
102	455.0687 (M + Na^+)	6.79	4.80	$C_{24}H_{16}O_8$	Kaempferol 3-*p*-coumarate	432.0845	Phenolics
103	399.2339	6.85	4.83	$C_{23}H_{30}N_2O_4$	Desacetoxyvindoline	398.2206	Alkaloids
104	446.2690 (M + NH_4^+)	6.93	7.66	$C_{24}H_{32}N_2O_5$	Aspidoalbine	428.2311	Alkaloids
105	371.2226 (M + CH3OH + H^+)	6.92	5.00	$C_{22}H_{26}O_3$	5,7-Dimethoxy-8-prenylflavan	338.1882	Flavonoids
106	384.1988 (M + NH_4^+)	6.98	10.99	$C_{19}H_{26}O_7$	Orizabin	366.1679	Terpenoids
107	435.1731	8.36	5.91	$C_{26}H_{26}O_6$	Cycloartocarpin A	434.1729	Flavonoids
108	309.1449	8.49	8.04	$C_{20}H_{20}O_3$	Isocordoin	308.1412	Phenolics
109	647.3895	8.74	11.05	$C_{36}H_{54}O_{10}$	Gypsogenin 3-O-b-D-glucuronide	646.3717	Terpenoids
110	354.1438 (M + Na^+)	8.96	5.61	$C_{22}H_{21}NO_2$	Melochinone	331.1572	Alkaloids
111	301.0489	9.00	5.91	$C_{12}H_{12}O_9$	Mumefural	300.0481	Furans
112	423.2096	9.20	6.47	$C_{26}H_{30}O_5$	Alopecurone G	422.2093	Flavonoids
113	415.1712	9.27	5.81	$C_{23}H_{26}O_7$	Heteroflavanone C	414.1679	Flavonoids
114	686.3632	9.39	9.61	$C_{36}H_{51}N_3O_{10}$	Avadharidine	685.3574	Terpenoids
115	415.2072	9.47	5.83	$C_{24}H_{30}O_6$	Armillaripin	414.2042	Terpenoids
116	387.1727	9.63	6.36	$C_{18}H_{26}O_9$	Methylsyringin	386.1577	Terpenoids
117	409.1384 (M + Na^+)	9.63	7.39	$C_{25}H_{22}O_4$	Fulvinervin B	386.1518	Flavonoids

Table 4 (continued)

Sr. No	Analyte Peak Name	Retention Time	Area / Height	Molecular formula	Compound name	Mass	Class of compound
118	229.1800	10.40	7.86	$C_{13}H_{24}O_3$	Menthone 1,2-glyceryl ketal	228.1725	Monoterpenoid
119	289.1581	10.51	7.16	$C_{16}H_{20}N_2O_3$	(±)-Rollipyrrole	288.1474	Alkaloids
120	423.2464	10.56	6.34	$C_{23}H_{34}O_7$	Picrasin C	422.2305	Terpenoids
121	281.2062	10.56	4.42	$C_{19}H_{24}N_2$	N-Methylaspidospermatidine	280.1939	Alkaloids
122	512.3634 ($M+NH_4^+$)	10.67	9.87	$C_{33}H_{42}N_4$	Auricularine	494.3409	Alkaloids
123	389.1716	10.62	7.30	$C_{25}H_{24}O_4$	Kanzonol E	388.1675	Flavonoids
124	531.3973 ($M+NH_4^+$)	10.80	9.25	$C_{18}H_{23}NO_4$	Pandamarilactonine A	317.1627	Alkaloids
125	322.2130	10.78	6.69	$C_{22}H_{27}NO$	Phenazocine	321.2093	Alkaloids
126	368.2188 ($M+NH_4^+$)	10.89	5.09	$C_{16}H_{30}O_6$	L-Citronellol glucoside	318.2042	Terpenoids
127	673.6284	10.96	14.58	$C_{23}H_{37}NO_5$	Cammaconine	407.2672	Terpenoids
128	397.2128	11.06	4.91	$C_{23}H_{28}N_2O_4$	Echitovenine	396.2049	Alkaloids
129	600.4545 ($M+NH_4^+$)	11.22	10.79	$C_{37}H_{58}O_5$	Hericene B	582.4284	Terpenoids
130	277.1950	11.27	5.58	$C_{16}H_{24}N_2O_2$	Carolinianine	276.1838	Alkaloids
131	694.3685 ($M+NH_4^+$)	11.29	5.20	$C_{36}H_{52}O_{12}$	Cucurbitacin I 2-glucoside	676.3459	Terpenoids
132	275.2372	11.44	8.66	$C_{19}H_{30}O$	4,5-(methanoxy-2-methylethano) isolongifol-4-ene	274.2297	Sesquiterpenoid
133	513.3911	11.29	9.54	$C_{33}H_{52}O_4$	Methyl 3b-hydroxy-13(18)-oleanen-28-oate	512.3866	Triterpenoid

components and biological activities of plant extracts. For this purpose, we conducted a multivariate analysis of the extracts tested. Initially, we assessed the correlation between the total bioactive compounds and the biological activities. As illustrated in Fig. 2A, the radical quenching and reducing potentials were strongly associated with these compounds. However, metal chelation and phosphomolybdenum capacities had no association with the total of phenolic and flavonoid components. This can be elucidated by the presence of non-phenolic substances like terpenoids or peptides. In agreement with our findings, several researchers highlighted a signficant relationship between the total bioactive constituents and antioxidant properties [68, 69]. In terms of enzyme inhibitory characteristics, no relationship was found with the total bioactive components. Principal component analysis was employed to demonstrate the similarity/dissimilarity among the tested samples and R^2 and O^2 that shows the fitness and predictive ability of the model were found as 0.98 and 0.82, respectively (Fig. 2B). In Fig. 2C, we observed a loading scatter plot of the tested variables, and the total bioactive components and antioxidant properties were the same in the plot. However, the enzyme inhibitory effects were classified in another plot. According to Fig. 2B and 2D, the tested extracts were classified into five groups. In comparison to the other extracts, the methanol extracts from both parts showed significantly stronger antioxidant activity, thereby setting them apart from the other extracts. At the same time, the chloroform extracts had a greater enzyme inhibition effect, thus leading them to be classified in the same group. It is clear that the plant parts and extraction solvents used influenced the distribution of extracts. Our findings can be utilized for further applications involving *T. falconeri*.

Post dock analysis

Among the docked compounds against acetylcholinesterase enzyme the ligand N-acetyldehydroanonaine and kanzonol E showed the highest binding affinity due to the lowest binding energies (-10.0 kcal/mol) compared to standard inhibitor (galantamine; -7.0 kcal/mol) (Fig. 3). Other ligands showed binding energies in the range -9.3 to -6.1 kcal/mol. While three ligands (quinic acid; -6.1, Rutacultin; -6.5, and Methylsyringin; -6.7 kcal/mol) showed binding affinity weaker than the standard (Table 5).

N-Acetyldehydroanonaine also showed the highest binding affinity among the docked ligands against butyrylcholinesterase enzyme (-10.9 kcal mol) (Fig. 4). Herein, murrayazolinine, kaempferol 3-*p*-coumarate, kanzonol, E castamollissin, brosimacutin C, isocordoin (binding energies; -10.6, -10.4, -9.8, -9.5, -9.3, and -9.3 kcal/mol respectively) exhibited their higher binding affinities towards the enzyme compared to galantamine

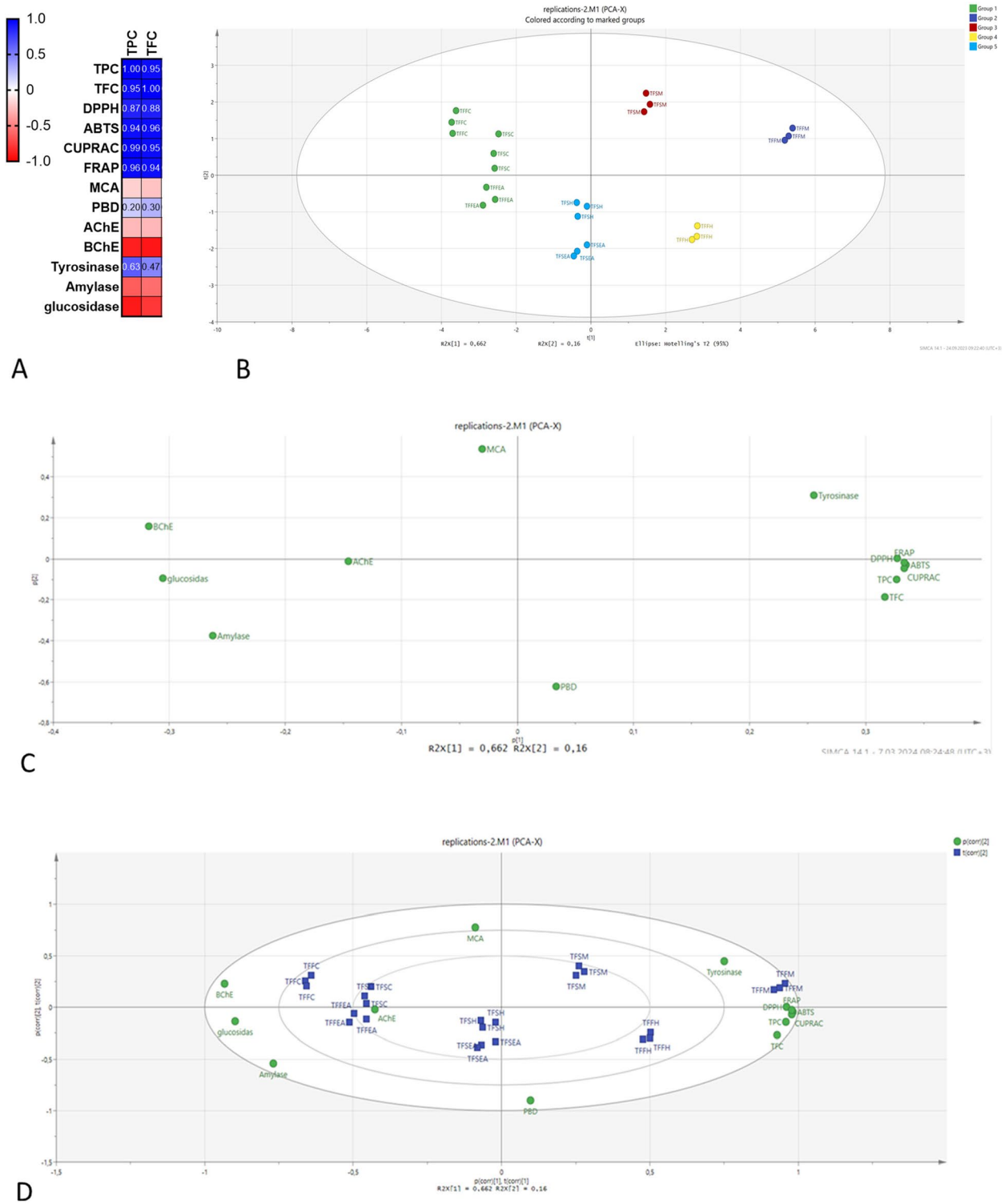

Fig. 2 (**A**) Pearson correlation values between biological activity assays ($p < 0.05$). TPC: Total phenolic content; TFC: Total flavonoid content; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid; DPPH: 1,1-diphenyl-2-picrylhydrazyl; CUPRAC: Cupric reducing antioxidant capacity; FRAP: Ferric reducing antioxidant power; AChE: acetylcholinesterase; BChE: butyrylcholinesterase. **B** A plot presentation of Principal component analysis between tested samples. **C** Loading scatter plot for variables. **D** Biplot presentation between variables and tested extracts. TFFM: methanolic extract of flower of *T. falconeri*; TFFH: hexane extract of flower of *T. falconeri*; TFFE: ethyl acetate extract of flower of *T. falconeri*; TFFC: chloroform extract of flower of *T. falconeri*; TFSM: methanolic extract of stem of *T. falconeri*; TFSH: hexane extract of stem of *T. falconeri*; TFSE: ethyl acetate extract of stem of *T. falconeri*; TFSC: methanolic extract of stem of *T. falconeri*

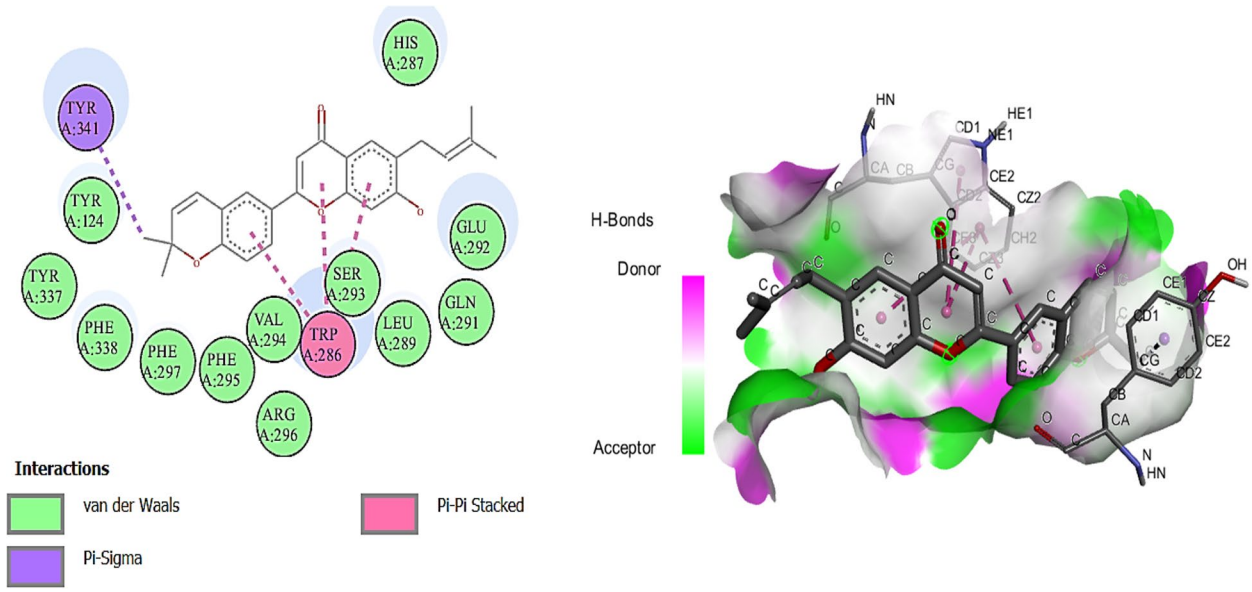

Fig. 3 Diagrammatic presentation of 2D (left) and 3D (right) interactions of Kanzonol E with acetylcholinesterase active site residues

Table 5 Binding energies of identified compounds after docking with enzymes

Sr.No	Compounds	AChE	BChE	α-Amylase	α-glucosidase	Tyrosinase
1	6-Caffeoylsucrose	-7.8	-8.8	-7.3	-8.1	-7.7
2	N-Acetyldehydroanonaine	-10.0	-10.9	-9.4	-8.7	-8.3
3	Bryaflavan	-8.0	-7.7	-8.0	-7.0	-7.2
4	Purpuritenin A	-8.6	-8.8	-7.9	-7.6	-6.7
5	3-O-Feruloylquinic acid	-7.5	-8.5	-7.8	-8.2	-6.9
6	Brosimacutin C	-8.5	-9.3	-8.7	-7.9	-7.5
7	Quinic acid	-6.1	-5.9	-5.8	-5.8	-5.3
8	Murrayazolinine	-9.0	-10.6	-9.0	-9,4	-8.1
9	Rutacultin	-6.5	-8.0	-7.0	-6.8	-6.6
10	Castamollissin	-9.2	-9.5	-8.6	-8.6	-8.1
11	9-Acetoxyfukinanolide	-7.7	-8.6	-7.3	-7.6	-6.2
12	Matteucinol	-9.3	8.1	-7.8	-7.4	-7.2
13	Kaempferol 3-*p*-coumarate	-8.7	-10.4	-8.5	-8.3	-9.0
14	Isocordoin	-8.9	-9.0	-8.4	-7.8	-7.3
15	Methylsyringin	-6.7	-7.0	-7.3	-7.3	-6.3
16	Kanzonol E	-10.0	-9.8	-9.6	-9.1	-8.7
17	Standard	-7.0a	-8.8a	-7.6b	-8.3b	-5.4c

Standards: Galantamine (a), acarbose (b), and kojic acid (c). While AChE and BChE represent the acetylcholinesterase and butyrylcholinesterase respectively

(-8.8 kcal/mol). While two compounds (6-caffeoylsucrose and purpuritenin A) were showing the binding affinity similar to the standard drug.

Eleven of the docked ligands showed α-amylase inhibitory properties due to their lower binding energies compared to acarbose (standard; -7.6 kcal/mol). Kanzonol E showed the highest binding affinity to bind with the enzyme compared to all other docked ligands due to its lowest biding energy (-9.6 kcal/mol) (Fig. 5). While, five ligands expressed more binding energies than standard drug and showed represent their less contribution in the inhibition of the enzyme.

Four compounds exhibited higher binding affinities when docked against the α-glucosidase enzyme, which attributes their contribution to the inhibitory effects of the plant extract. Murrayazolinine showed

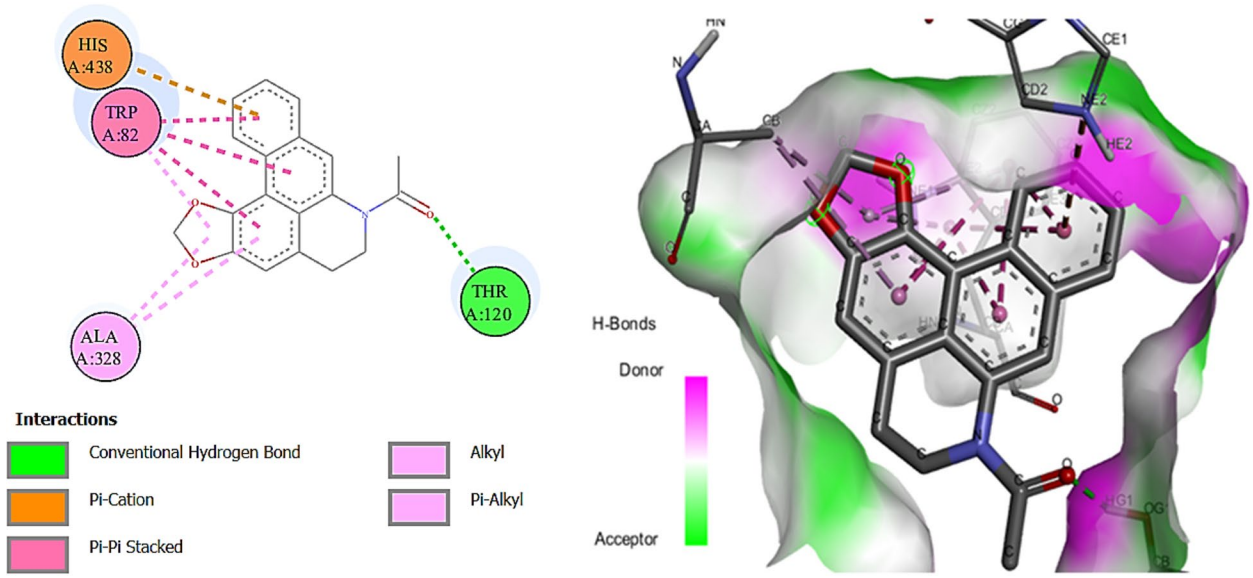

Fig. 4 Diagrammatic presentation of 2D (left) and 3D (right) interactions of N-acetyldehydroanonaine E with butyrylcholinesterase active site residues

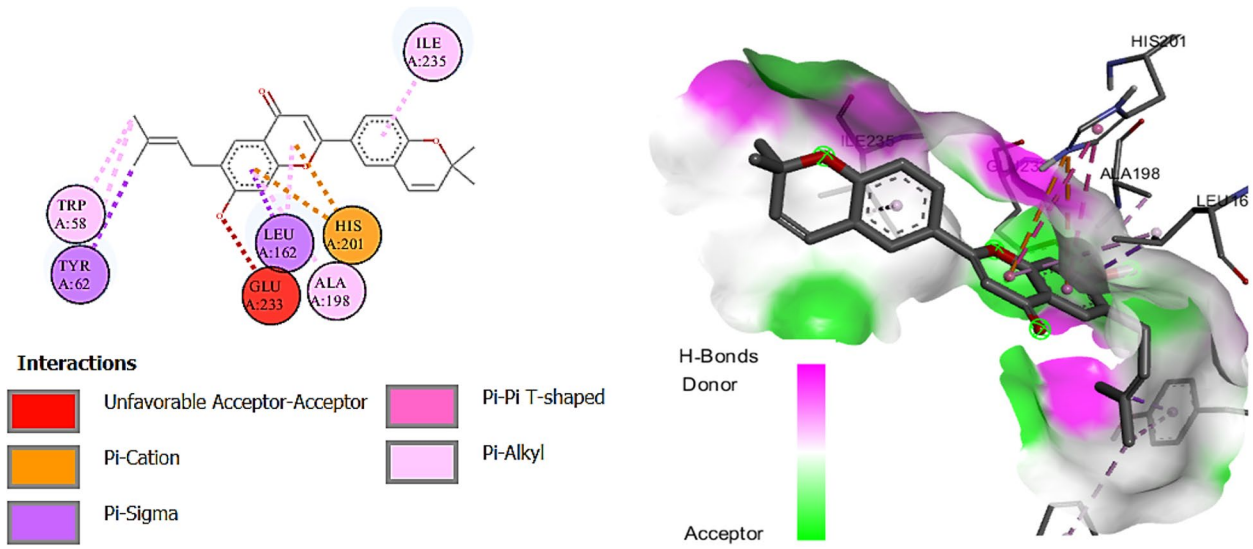

Fig. 5 Diagrammatic presentation of 2D (left) and 3D (right) interactions of Kanzonol E with α-amylase active site residues

the highest binding affinity due to -9.4 kcal binding energy compared to the standard inhibitor (acarbose; -8.3 kcal/mol) (Fig. 6), while the compounds kanzonol E (-9.1), N-acetyldehydroanonaine (-8.7), and castamollissin (-8.6) also showed better binding than acarbose. Moreover, kaempferol 3-*p*-coumarate depicted similar binding affinity to the standard and all the remaining compounds showed lesser affinity due to their higher binding energies (-5.8 to -8.2 kcal/mol) than the standard drug.

For tyrosinase inhibition only quinic acid (-5.3 kcal/mol) showed lesser binding compared to the kojic acid (-5.4 kcal/mol) used as standard tyrosinase inhibitor. While, all the other docked ligands exhibited lower binding energies (-6.2 to -9.0 kcal/mol) showing their possible contribution in the tyrosinase inhibitory properties of the extract. The results further showed that kaempferol 3-*p*-coumarate has highest binding affinity towards tyrosinase enzyme due to its lowest binding energy (-9.0 kcal/mol) (Fig. 7).

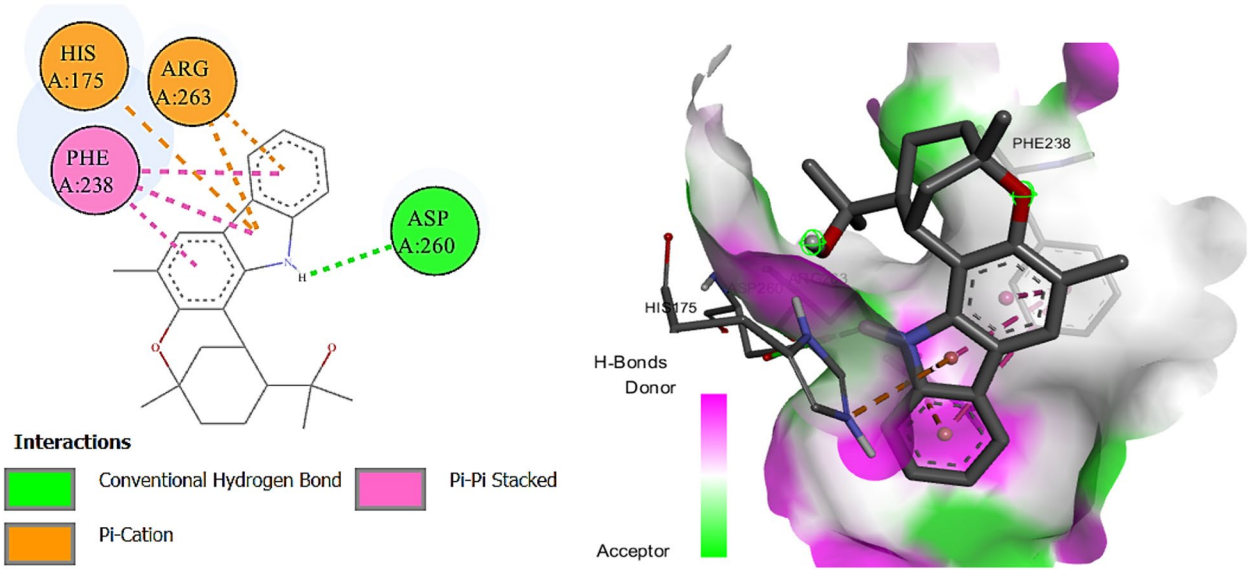

Fig. 6 Diagrammatic presentation of 2D (left) and 3D (right) interactions of murrayazolinine with α-glucosidase active site residues

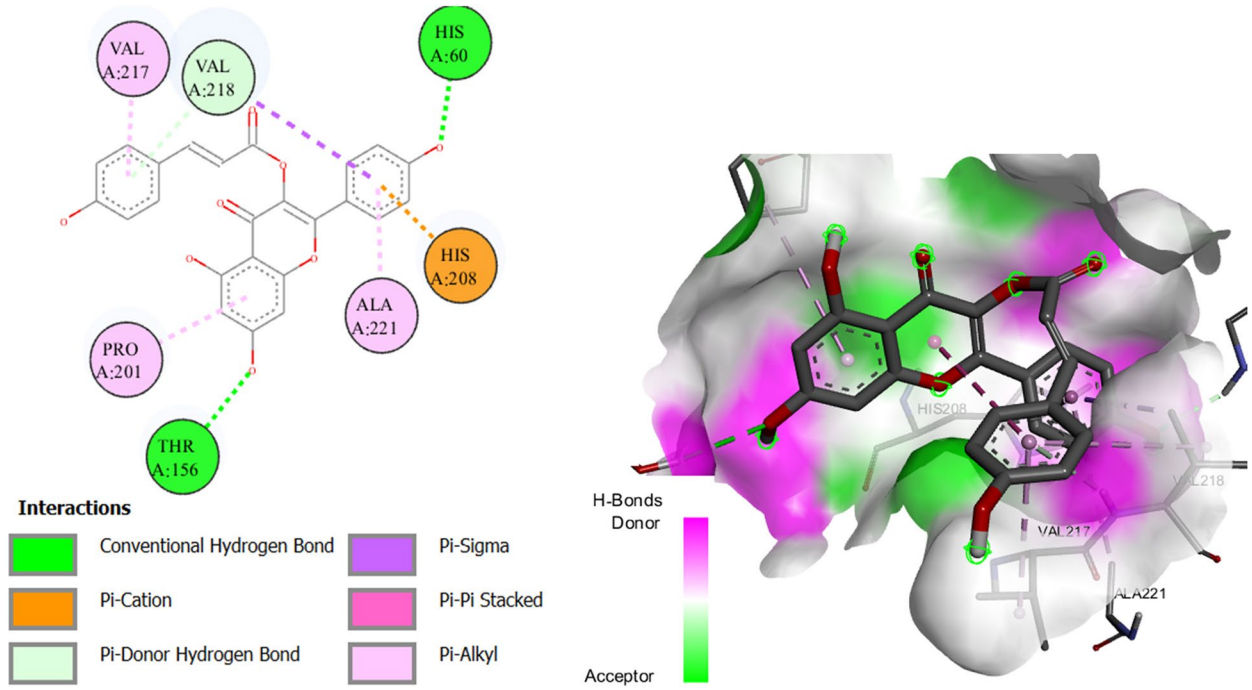

Fig. 7 Diagrammatic presentation of 2D (left) and 3D (right) interactions of kaempferol 3-p-coumarate with tyrosinase active site residues

ADME Analysis

The information anticipated for the medicinal chemistry, pharmacokinetics, lipophilicity, physicochemical properties, solubility, and drug resemblance of compounds assessed by SwissADME [70] is provided in Table 6. The molecular weights of the docked compounds were found within the range of 200–600 Da and to be 192.17–504.44, based on Lipinski's rule of five. The logP values were between -0.12 to 4.42, which were less than 5. All of the compound's products had an HBA number of 2 to 9 except for two compounds 6-caffeoylsucrose and castamollissin

Table 6 Medicinal and Drug-like properties of selected compounds predicted using SwissADME

Compounds	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
6-Caffeoylsucrose	Formula: $C_{21}H_{28}O_{14}$ Molecular weight: 504.44 g/mol Num. heavy atoms: 35 Num. arom. heavy atoms: 6 Fraction Csp3: 0.57 Num. rotatable bonds: 9 Num. H-bond acceptors: 14 Num. H-bond donors:9 Molar Refractivity: 111.55 TPSA: 236.06	Log Po/w (iLOGP): 1.77 Log Po/w (XLOGP3): -2.30 Log Po/w (WLOGP): -3.83 Log Po/w (MLOGP): -3.59 Log Po/w (SILICOS-IT): -2.65 Consensus Log Po/w: -2.12	Log S (ESOL): -1.05 Solubility: 4.48e + 01 mg/ml; 8.88e-02 mol/l Class: Very soluble Log S (Ali): -2.12 Solubility: 3.81e + 00 mg/ml; 7.56e-03 mol/l Class: Soluble Log S (SILICOS-IT): 2.10 Solubility: 6.39e + 04 mg/ml; 1.27e + 02 mol/l Class: Soluble	GI absorption: Low BBB permeant: No P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -11.01 cm/s	Lipinski: No; 3 violations: MW > 500, NorO > 10, NHorOH > 5 Ghose: No; 2 violations: MW > 480, WLOGP < -0.4 Veber: No; 1 violation: TPSA > 140 Egan: No; 1 violation: TPSA > 131.6 Muegge: No; 4 violations: XLOGP3 < -2, TPSA > 150, H-acc > 10, H-don > 5 Bioavailability Score: 0.17	PAINS: 1 alert: catechol_A Brenk: 2 alerts: catechol, michael_acceptor_1 Leadlikeness: No; 2 violations: MW > 350, Rotors > 7 Synthetic accessibility: 5.56
N-Acetyldehydroanonaine	Formula: $C_{19}H_{15}NO_3$ SMolecular weight: 305.33 g/mol Num. heavy atoms: 23 Num. arom. heavy atoms: 14 Fraction Csp3: 0.21 Num. rotatable bonds: 1 Num. H-bond acceptors: 3 Num. H-bond donors: 0 Molar Refractivity: 92.52 TPSA: 38.77	Log Po/w (iLOGP): 2.93 Log Po/w (XLOGP3): 3.63 Log Po/w (WLOGP): 3.25 Log Po/w (MLOGP): 2.89 Log Po/w (SILICOS-IT): 3.88 Consensus Log Po/w: 3.32	Log S (ESOL): -4.40 Solubility: 1.20e-02 mg/ml; 3.94e-05 mol/l Class: Moderately soluble Log S (Ali): -4.13 Solubility: 2.25e-02 mg/ml; 7.38e-05 mol/l Class: Moderately soluble Log S (SILICOS-IT): -5.71 Solubility: 5.94e-04 mg/ml; 1.95e-06 mol/l Class: Moderately soluble	GI absorption: High BBB permeant: Yes P-gp substrate: Yes CYP1A2 inhibitor: Yes CYP2C19 inhibitor: Yes CYP2C9 inhibitor: Yes CYP2D6 inhibitor: No CYP3A4 inhibitor: Yes Log Kp (skin permeation): -5.59 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 1 alert: polycyclic_aromatic_hydrocarbon_3 Leadlikeness: No; 1 violation: XLOGP3 > 3.5 Synthetic accessibility: 2.53
Bryaflavan	Formula: $C_{17}H_{18}O_6$ Molecular weight: 318.32 g/mol Num. heavy atoms: 23 Num. arom. heavy atoms: 12 Fraction Csp3: 0.29 Num. rotatable bonds: 3 Num. H-bond acceptors: 6 Num. H-bond donors:3 Molar Refractivity: 84.13 TPSA: 88.38	Log Po/w (iLOGP): 2.43 Log Po/w (XLOGP3): 2.55 Log Po/w (WLOGP): 2.54 Log Po/w (MLOGP): 1.00 Log Po/w (SILICOS-IT): 2.44 Consensus Log Po/w: 2.19	Log S (ESOL): -3.61 Solubility: 7.85e-02 mg/ml; 2.47e-04 mol/l Class: Soluble Log S (Ali): -4.05 Solubility: 2.82e-02 mg/ml; 8.84e-05 mol/l Class: Moderately soluble Log S (SILICOS-IT): -3.77 Solubility: 5.47e-02 mg/ml; 1.72e-04 mol/l Class: Soluble	GI absorption: High BBB permeant: No P-gp substrate: Yes CYP1A2 inhibitor: Yes CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: Yes CYP3A4 inhibitor: Yes Log Kp (skin permeation): -6.43 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 1 alert: catechol_A Brenk: 1 alert: catechol Leadlikeness: Yes Synthetic accessibility: 3.41

Table 6 (continued)

Compounds	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
Purpuritenin A	Formula: $C_{19}H_{16}O_3$ Molecular weight: 292.33 g/mol Num. heavy atoms: 22 Num. arom. heavy atoms: 15 Fraction Csp3: 0.11 Num. rotatable bonds: 4 Num. H-bond acceptors: 3 Num. H-bond donors: 0 Molar Refractivity: 87.48 TPSA: 39.44	Log Po/w (iLOGP): 3.14 Log Po/w (XLOGP3): 4.43 Log Po/w (WLOGP): 4.54 Log Po/w (MLOGP): 2.59 Log Po/w (SILICOS-IT): 4.94 Consensus Log Po/w: 3.93	Log S (ESOL): -4.68 Solubility: 6.05e-03 mg/ml; 2.07e-05 mol/l Class: Moderately soluble Log S (Ali): -4.98 Solubility: 3.09e-03 mg/ml; 1.06e-05 mol/l Class: Moderately soluble Log S (SILICOS-IT): -6.35 Solubility: 1.31e-04 mg/ml; 4.47e-07 mol/l Class: Poorly soluble	GI absorption: High BBB permeant: Yes P-gp substrate: No CYP1A2 inhibitor: Yes CYP2C19 inhibitor: Yes CYP2C9 inhibitor: Yes CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -4.94 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 1 alert: michael_acceptor_1 Leadlikeness: No; 1 violation: XLOGP3 > 3.5 Synthetic accessibility: 3.13
3-O-Feruloylquinic acid	Formula: $C_{17}H_{20}O_9$ Molecular weight: 368.34 g/mol Num. heavy atoms: 26 Num. arom. heavy atoms: 6 Fraction Csp3: 0.41 Num. rotatable bonds: 6 Num. H-bond acceptors: 9 Num. H-bond donors: 5 Molar Refractivity: 87.97 TPSA: 153.75	Log Po/w (iLOGP): 1.47 Log Po/w (XLOGP3): -0.10 Log Po/w (WLOGP): -0.45 Log Po/w (MLOGP): -0.81 Log Po/w (SILICOS-IT): -0.07 Consensus Log Po/w: 0.01:	Log S (ESOL): -1.84 Solubility: 5.38e+00 mg/ml; 1.46e-02 mol/l Class: Very soluble Log S (Ali): -2.68 Solubility: 7.76e-01 mg/ml; 2.11e-03 mol/l Class: Soluble Log S (SILICOS-IT): -0.29 Solubility: 1.89e+02 mg/ml; 5.13e-01 mol/l Class: Soluble	GI absorption: Low BBB permeant: No P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -8.62 cm/s	Lipinski: Yes; 0 violation Ghose: No; 1 violation: WLOGP < -0.4 Veber: No; 1 violation: TPSA > 140 Egan: No; 1 violation: TPSA > 131.6 Muegge: No; 1 violation: TPSA > 150 Bioavailability Score: 0.11	PAINS: 0 alert Brenk: 1 alert: michael_acceptor_1 Leadlikeness: No; 1 violation: MW > 350 Synthetic accessibility: 4.25
Brosimacutin C	Formula: $C_{20}H_{22}O_5$ Molecular weight: 342.39 g/mol Num. heavy atoms: 25 Num. arom. heavy atoms: 12 Fraction Csp3: 0.35 Num. rotatable bonds: 4 Num. H-bond acceptors: 5 Num. H-bond donors: 3 Molar Refractivity: 94.94 TPSA: 86.99	Log Po/w (iLOGP): 2.62 Log Po/w (XLOGP3): 2.75 Log Po/w (WLOGP): 3.18 Log Po/w (MLOGP): 1.63 Log Po/w (SILICOS-IT): 3.62 Consensus Log Po/w: 2.76	Log S (ESOL): -3.79 Solubility: 5.60e-02 mg/ml; 1.63e-04 mol/l Class: Soluble Log S (Ali): -4.23 Solubility: 2.01e-02 mg/ml; 5.87e-05 mol/l Class: Moderately soluble Log S (SILICOS-IT): -5.02 Solubility: 3.30e-03 mg/ml; 9.64e-06 mol/l Class: Moderately soluble	GI absorption: High BBB permeant: No P-gp substrate: Yes CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: Yes CYP3A4 inhibitor: No Log Kp (skin permeation): -6.44 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 0 alert Leadlikeness: Yes Synthetic accessibility: 3.61

Table 6 (continued)

Compounds	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
Quinic acid	Formula: $C_7H_{12}O_6$ Molecular weight: 192.17 g/mol Num. heavy atoms: 13 Num. arom. heavy atoms: 0 Fraction Csp3: 0.86 Num. rotatable bonds: 1 Num. H-bond acceptors: 6 Num. H-bond donors: 5 Molar Refractivity: 40.11 TPSA: 118.22	Log Po/w (iLOGP): -0.12 Log Po/w (XLOGP3): -2.37 Log Po/w (WLOGP): -2.32 Log Po/w (MLOGP): -2.14 Log Po/w (SILICOS-IT): -1.82 Consensus Log Po/w: -1.75	Log S (ESOL): 0.53 Solubility: 6.48e + 02 mg/ml; 3.37e + 00 mol/l Class: Highly soluble Log S (Ali): 0.43 Solubility: 5.12e + 02 mg/ml; 2.66e + 00 mol/l Class: Highly soluble Log S (SILICOS-IT): 2.08 Solubility: 2.30e + 04 mg/ml; 1.20e + 02 mol/l Class: Soluble	GI absorption: Low BBB permeant: No P-gp substrate: Yes CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -9.15 cm/s	Lipinski: Yes; 0 violation Ghose: No; 1 violation: WLOGP < -0.4 Veber: Yes Egan: Yes Muegge: No; 2 violations: MW < 200, XLOGP3 < -2 Bioavailability Score: 0.56	PAINS: 0 alert Brenk: 0 alert Leadlikeness: No; 1 violation: MW < 250 Synthetic accessibility: 3.34
Murrayazolinine	Formula: $C_{23}H_{27}NO_2$ Molecular weight: 349.47 g/mol Num. heavy atoms: 26 Num. arom. heavy atoms: 13 Fraction Csp3: 0.48 Num. rotatable bonds: 1 Num. H-bond acceptors: 2 Num. H-bond donors: 2 Molar Refractivity: 107.69 TPSA: 45.25	Log Po/w (iLOGP): 3.42 Log Po/w (XLOGP3): 4.84 Log Po/w (WLOGP): 5.44 Log Po/w (MLOGP): 3.93 Log Po/w (SILICOS-IT): 5.46 Consensus Log Po/w: 4.62	Log S (ESOL): -5.36 Solubility: 1.53e-03 mg/ml; 4.37e-06 mol/l Class: Moderately soluble Log S (Ali): -5.52 Solubility: 1.05e-03 mg/ml; 2.99e-06 mol/l Class: Moderately soluble Log S (SILICOS-IT): -6.87 Solubility: 4.71e-05 mg/ml; 1.35e-07 mol/l Class: Poorly soluble	GI absorption: High BBB permeant: Yes P-gp substrate: Yes CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: Yes CYP3A4 inhibitor: No Log Kp (skin permeation): -5.00 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 0 alert Leadlikeness: No; 1 violation: XLOGP3 > 3.5 Synthetic accessibility: 4.53
Rutacultin	Formula: $C_{16}H_{18}O_4$ Molecular weight: 274.31 g/mol Num. heavy atoms: 20 Num. arom. heavy atoms: 10 Fraction Csp3: 0.31 Num. rotatable bonds: 4 Num. H-bond acceptors: 4 Num. H-bond donors: 0 Molar Refractivity: 79.07 TPSA: 48.67	Log Po/w (iLOGP): 3.25 Log Po/w (XLOGP3): 3.81 Log Po/w (WLOGP): 3.27 Log Po/w (MLOGP): 2.29 Log Po/w (SILICOS-IT): 4.09 Consensus Log Po/w: 3.34	Log S (ESOL): -4.05 Solubility: 2.46e-02 mg/ml; 8.97e-05 mol/l Class: Moderately soluble Log S (Ali): -4.53 Solubility: 8.15e-03 mg/ml; 2.97e-05 mol/l Class: Moderately soluble Log S (SILICOS-IT): -5.13 Solubility: 2.01e-03 mg/ml; 7.33e-06 mol/l Class: Moderately soluble	GI absorption: High BBB permeant: Yes P-gp substrate: No CYP1A2 inhibitor: Yes CYP2C19 inhibitor: Yes CYP2C9 inhibitor: Yes CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -5.27 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 2 alerts: cumarine, isolated_alkene Leadlikeness: No; 1 violation: XLOGP3 > 3.5 Synthetic accessibility: 3.27

Table 6 (continued)

Compounds	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
Castamollissin	Formula: $C_{20}H_{20}O_{13}$ Molecular weight: 468.37 g/mol Num. heavy atoms: 33 Num. arom. heavy atoms: 12 Fraction Csp3: 0.30 Num. rotatable bonds: 7 Num. H-bond acceptors: 13 Num. H-bond donors: 8 Molar Refractivity: 105.73 TPSA: 223.67 $Å^2$	Log Po/w (iLOGP): 0.93 Log Po/w (XLOGP3): -0.87 Log Po/w (WLOGP): -0.93 Log Po/w (MLOGP): -2.37 Log Po/w (SILICOS-IT): -1.34 Consensus Log Po/w: -0.92	Log S (ESOL): -2.00 Solubility: 4.65e + 00 mg/ml; 9.93e-03 mol/l Class: Soluble Log S (Ali): -3.35 Solubility: 2.11e-01 mg/ml; 4.51e-04 mol/l Class: Soluble Log S (SILICOS-IT): 0.07 Solubility: 5.49e + 02 mg/ml; 1.17e + 00 mol/l Class: Soluble	GI absorption: Low BBB permeant: No P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -9.77 cm/s	Lipinski: No; 2 violations: NorO > 10, NHorOH > 5 Ghose: No; 1 violation: WLOGP < -0.4 Veber: No; 1 violation: TPSA > 140 Egan: No; 1 violation: TPSA > 131.6 Muegge: No; 3 violations: TPSA > 150, H-acc > 10, H-don > 5 Bioavailability Score: 0.17	PAINS: 1 alert: catechol_A Brenk: 2 alerts: aldehyde, catechol Leadlikeness: No; 1 violation: MW > 350 Synthetic accessibility: 4.88
9-Acetoxyfukinanolide	Formula: $C_{17}H_{24}O_4$ Molecular weight: 292.37 g/mol Num. heavy atoms: 21 Num. arom. heavy atoms: 0 Fraction Csp3: 0.76 Num. rotatable bonds: 2 Num. H-bond acceptors: 4 Num. H-bond donors: 0 Molar Refractivity: 79.07 TPSA: 52.60 $Å^2$	Log Po/w (iLOGP): 2.48 Log Po/w (XLOGP3): 2.92 Log Po/w (WLOGP): 2.86 Log Po/w (MLOGP): 2.92 Log Po/w (SILICOS-IT): 3.18 Consensus Log Po/w: 2.87	Log S (ESOL): -3.36 Solubility: 1.28e-01 mg/ml; 4.36e-04 mol/l Class: Soluble Log S (Ali): -3.69 Solubility: 6.03e-02 mg/ml; 2.06e-04 mol/l Class: Soluble Log S (SILICOS-IT): -3.35 Solubility: 1.30e-01 mg/ml; 4.45e-04 mol/l Class: Soluble	GI absorption: High BBB permeant: Yes P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -6.01 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 2 alerts: isolated_alkene, more_than_2_esters Leadlikeness: Yes Synthetic accessibility: 4.88
Matteucinol	Formula: $C_{18}H_{18}O_5$ Molecular weight: 314.33 g/mol Num. heavy atoms: 23 Num. arom. heavy atoms: 12 Fraction Csp3: 0.28 Num. rotatable bonds: 2 Num. H-bond acceptors: 5 Num. H-bond donors: 2 Molar Refractivity: 85.97 TPSA: 75.99 $Å^2$	Log Po/w (iLOGP): 2.95 Log Po/w (XLOGP3): 3.45 Log Po/w (WLOGP): 3.11 Log Po/w (MLOGP): 1.44 Log Po/w (SILICOS-IT): 3.58 Consensus Log Po/w: 2.91	Log S (ESOL): -4.22 Solubility: 1.91e-02 mg/ml; 6.08e-05 mol/l Class: Moderately soluble Log S (Ali): -4.73 Solubility: 5.89e-03 mg/ml; 1.87e-05 mol/l Class: Moderately soluble Log S (SILICOS-IT): -4.88 Solubility: 4.16e-03 mg/ml; 1.32e-05 mol/l Class: Moderately soluble	GI absorption: High BBB permeant: Yes P-gp substrate: No CYP1A2 inhibitor: Yes CYP2C19 inhibitor: Yes CYP2C9 inhibitor: Yes CYP2D6 inhibitor: Yes CYP3A4 inhibitor: Yes Log Kp (skin permeation): -5.77 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 0 alert Leadlikeness: Yes Synthetic accessibility: 3.37

Table 6 (continued)

Compounds	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
Kaempferol 3-*p*-coumarate	Formula: $C_{24}H_{16}O_8$ Molecular weight: 432.38 g/mol Num. heavy atoms: 32 Num. arom. heavy atoms: 22 Fraction Csp3: 0.00 Num. rotatable bonds: 5 Num. H-bond acceptors: 8 Num. H-bond donors: 4 Molar Refractivity: 117.12 TPSA: 137.43 $Å^2$	Log Po/w (iLOGP): 2.67 Log Po/w (XLOGP3): 4.36 Log Po/w (WLOGP): 3.79 Log Po/w (MLOGP): 1.17 Log Po/w (SILICOS-IT): 3.65 Consensus Log Po/w: 3.13	Log S (ESOL): -5.45 Solubility: 1.55e-03 mg/ml; 3.58e-06 mol/l Class: Moderately soluble Log S (Ali): -6.96 Solubility: 4.72e-05 mg/ml; 1.09e-07 mol/l Class: Poorly soluble Log S (SILICOS-IT): -6.02 Solubility: 4.16e-04 mg/ml; 9.62e-07 mol/l Class: Poorly soluble	GI absorption: Low BBB permeant: No P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: Yes CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -5.84 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: No; 1 violation: TPSA > 131.6 Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 1 alert: michael_acceptor_1 Leadlikeness: No; 2 violations: MW > 350, XLOGP3 > 3.5 Synthetic accessibility: 3.79
Isocordoin	Formula: $C_{20}H_{20}O_3$ Molecular weight: 308.37 g/mol Num. heavy atoms: 23 Num. arom. heavy atoms: 12 Fraction Csp3: 0.15 Num. rotatable bonds: 5 Num. H-bond acceptors: 3 Num. H-bond donors: 2 Molar Refractivity: 94.01 TPSA: 57.53 $Å^{22}$	Log Po/w (iLOGP): 3.39 Log Po/w (XLOGP3): 5.46 Log Po/w (WLOGP): 4.39 Log Po/w (MLOGP): 3.28 Log Po/w (SILICOS-IT): 4.70 Consensus Log Po/w: 4.24	Log S (ESOL): -5.25 Solubility: 1.74e-03 mg/ml; 5.65e-06 mol/l Class: Moderately soluble Log S (Ali): -6.43 Solubility: 1.16e-04 mg/ml; 3.76e-07 mol/l Class: Poorly soluble Log S (SILICOS-IT): -5.06 Solubility: 2.70e-03 mg/ml; 8.77e-06 mol/l Class: Moderately soluble	GI absorption: High BBB permeant: Yes P-gp substrate: No CYP1A2 inhibitor: Yes CYP2C19 inhibitor: Yes CYP2C9 inhibitor: Yes CYP2D6 inhibitor: No CYP3A4 inhibitor: Yes Log Kp (skin permeation): -4.30 cm/s	Lipinski: Yes; 0 violation Ghose: Yes Veber: Yes Egan: Yes Muegge: No; 1 violation: XLOGP3 > 5 Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 2 alerts: isolated_alkene, michael_acceptor_1 Leadlikeness: No; 1 violation: XLOGP3 > 3.5 Synthetic accessibility: 2.99
Methylsyringin	Formula: $C_{18}H_{26}O_9$ Molecular weight: 386.39 g/mol Num. heavy atoms: 27 Num. arom. heavy atoms: 6 Fraction Csp3: 0.56 Num. rotatable bonds: 8 Num. H-bond acceptors: 9 Num. H-bond donors: 4 Molar Refractivity: 94.36 TPSA: 127.07 $Å^2$	Log Po/w (iLOGP): 2.46 Log Po/w (XLOGP3): -0.77 Log Po/w (WLOGP): -0.57 Log Po/w (MLOGP): -1.35 Log Po/w (SILICOS-IT): 0.42 Consensus Log Po/w: 0.04	Log S (ESOL): -1.39 Solubility: 1.59e+01 mg/ml; 4.10e-02 mol/l Class: Very soluble Log S (Ali): -1.42 Solubility: 1.47e+01 mg/ml; 3.80e-02 mol/l Class: Very soluble Log S (SILICOS-IT): -1.03 Solubility: 3.61e+01 mg/ml; 9.33e-02 mol/l Class: Soluble	GI absorption: High BBB permeant: No P-gp substrate: Yes CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -9.20 cm/s	Lipinski: Yes; 0 violation Ghose: No; 1 violation: WLOGP < -0.4 Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 0 alert Leadlikeness: No; 2 violations: MW > 350, Rotors > 7 Synthetic accessibility: 4.88

Table 6 (continued)

Compounds	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
Kanzonol E	Formula: $C_{25}H_{24}O_4$ Molecular weight: 388.46 g/mol Num. heavy atoms: 29 Num. arom. heavy atoms: 16 Fraction Csp3: 0.24 Num. rotatable bonds: 3 Num. H-bond acceptors: 4 Num. H-bond donors: 1 Molar Refractivity: 117.78 TPSA: 59.67 Å^2	Log Po/w (iLOGP): 4.24 Log Po/w (XLOGP3): 5.67 Log Po/w (WLOGP): 5.75 Log Po/w (MLOGP): 3.20 Log Po/w (SILICOS-IT): 6.14 Consensus Log Po/w: 5.00	Log S (ESOL): -6.03 Solubility: 3.62e-04 mg/ml; 9.32e-07 mol/l Class: Poorly soluble Log S (Ali): -6.69 Solubility: 7.97e-05 mg/ml; 2.05e-07 mol/l Class: Poorly soluble Log S (SILICOS-IT): -7.62 Solubility: 9.34e-06 mg/ml; 2.40e-08 mol/l Class: Poorly soluble	GI absorption: High BBB permeant: No P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: Yes CYP2C9 inhibitor: Yes CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log Kp (skin permeation): -4.64 cm/s	Lipinski: Yes; 0 violation Ghose: No; 1 violation: WLOGP > 5.6 Veber: Yes Egan: Yes Muegge: No; 1 violation: XLOGP3 > 5 Bioavailability Score: 0.55	PAINS: 0 alert Brenk: 1 alert: isolated_alkene Leadlikeness: No; 2 violations: MW > 350, XLOGP3 > 3.5 Synthetic accessibility: 4.14

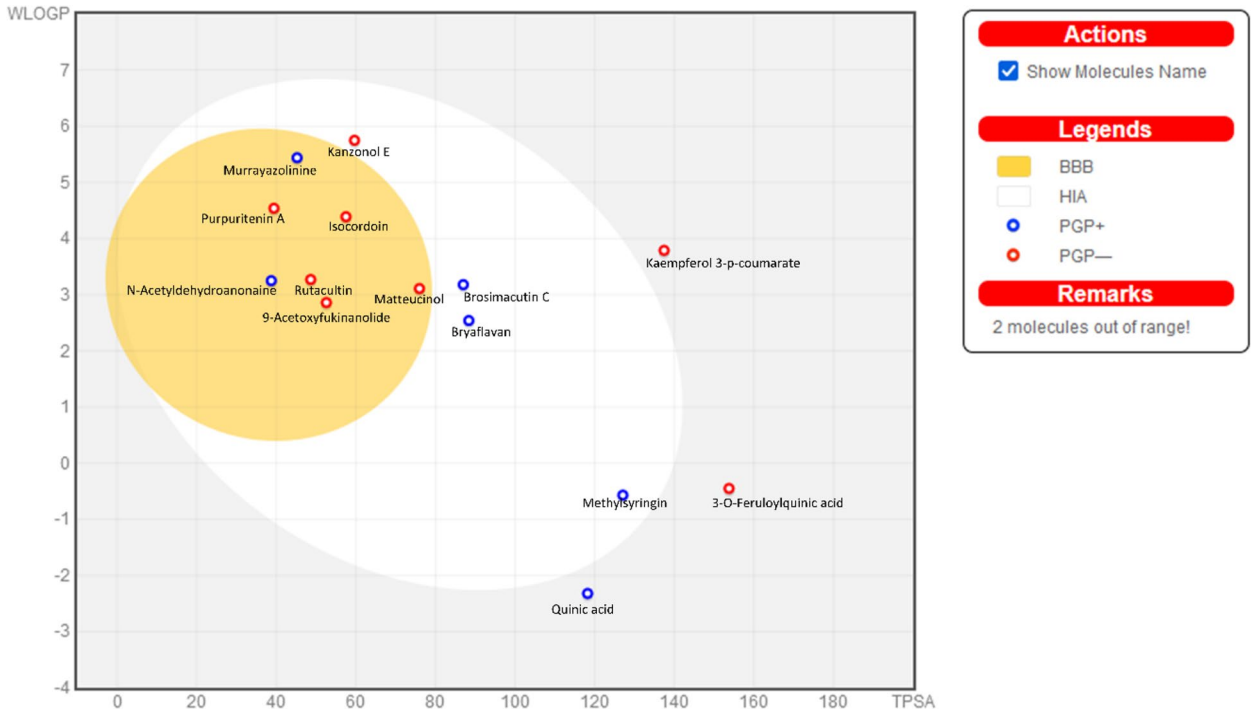

Fig. 8 Graphical Distribution of compounds according to predicted model of BOILED-Egg

which can accept 14 and 13 HBA respectively. While the same trend was observed for HBD numbers the two compounds have HBD numbers 9 and 8 respectively while the remaining compounds have HBD numbers ≤ 5 [71]. The graphical model known as the Brain Or IntestinaL EstimateD Permeation (BOILED-Egg) technique determines the polarity and lipophilicity of small compounds. Concerning the possibility of oral absorption of medication candidates, this prediction offers a visual cue for the synthesis design of novel compounds [72]. Figure 8 displays a graphic estimate of these selectively docked compounds' gastrointestinal absorption and blood–brain barrier (BBB) penetration. The compounds N-Acetyldehydroanonaine, Purpuritenin A, Murrayazolinine, Rutacultin, 9-Acetoxyfukinanolide and Matteucinol were found in the BBB, while Bryaflavan, Brosimacutin C, Methylsyringin and Kanzonol E were found in white region. The white region contains those compounds which have good potential to be absorbed through the gastrointestinal tract. The compounds 3-O-Feruloylquinic acid, Quinic acid and Kaempferol 3-*p*-coumarate as indicated by the BOILED-Egg plot were presented in gray region. The gray region is designated for poor intestine absorption. The two compounds 6-caffeoylsucrose and castamollissin violated Lipinski's rule and were not shown in BOILED-Egg The compounds showed with blue spot, was discovered to be indicative of their high bioavailability. The compounds Bryaflavan, Brosimacutin C, Methylsyringin and Kanzonol E show great promise as gastrointestinal tract absorbers since they do not cross the blood–brain barrier. These substances have no adverse effects on central nervous system depression or sleepiness because they cannot penetrate the blood–brain barrier.

Acknowledgements
The authors would like to extend their sincere appreciation to the Researchers Supporting Project Number (RSP2024R356), King Saud University, Riyadh, Saudi Arabia.

Code availability
Not applicable.

Authors' contributions
MIT, ZA, MN, MS designed the concept the paper, writing and performed the chemical part. AT, AH, SA, MA performed molecular dockig analysis and ADME studies JK, GZ performed biological activity assays. AH, KFA, GDA, EFA writing, reviewing and editing. All authors read and agreed to the published version of the manuscript.

Funding
The authors would like to extend their sincere appreciation to the Researchers Supporting Project Number (RSP2024R356), King Saud University, Riyadh, Saudi Arabia.

Availability of data and materials
The datasets used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 30 December 2023 Accepted: 27 March 2024
Published online: 22 April 2024

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