HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

الجمعية السعودية لعلوم الحياة
SAUDI BIOLOGICAL SOCIETY

Original article

In silico analysis of selected nutrition rich fruit of Bunch berry (*Lantana camara*) constituents as human acetylcholinesterase (hAchE), carbonic anhydrase II (hCA-II) and carboxylesterase 1 (hCES-1) inhibitory agents

V. Surya Prakash [a,1], N. Radhakrishnan [a,1,*], P. Vasantha-Srinivasan [b], Chinnadurai Veeramani [c], Ahmed S. El Newehy [c], Mohammed A. Alsaif [c], Khalid S. Al-Numair [c]

[a] *Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Chennai, Tamil Nadu 602 105, India*
[b] *Department of Bio-Informatics, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Chennai 602105, India*
[c] *Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, P.O. Box 10219, Riyadh 11433, Saudi Arabia*

ARTICLE INFO

Keywords:
Bunch berry
Lantana camara
Docking
Human acetylcholinesterase (hAchE)
Human carbonic anhydrase II (hCA-II)
Human carboxylesterase I (hCES-I)

ABSTRACT

Background: Bunch berry (*Lantana camara*) is primarily composed of flavonoids and vitamin C; therefore, it has been shown to possess various medical characteristics, including the ability to relieve fever, inflammation, and urinary tract infections.
Objective: In this study, we intended to assess twenty chosen constituents of Bunch berry as potent inhibitory agents of human acetylcholinesterase (hAchE), carbonic anhydrase II (hCA-II) and carboxylesterase 1 (hCES-1) employing in *silico* techniques.
Methods: The twenty chosen Bunch berry components were examined about docking behaviour of hAchE, hCA-II and hCES-I by using the Swissdock method. Apart from to docking, Molecular physico-chemical, drug-likeness, ADME (ingesting, dispersing, metabolising, and excreting), and toxicity assessments were also performed utilising the Molinspiration, Swiss ADME, pkCSM, and STITCH web sites, correspondingly.
Results: Eight ligands (40 %) have exhibited strict adherence to Lipinski's rule of five (Ro5), according to molecular physico-chemical study. Drug-likeness property analysis has shown that five ligands (25 %) of Bunch berry predicted to exhibit moderate bioactivity score against all the descriptors. ADME analysis has shown that five ligands (25 %) of Bunch berry are predicted to possess high gastrointestinal absorption property Toxicity analysis has shown that six ligands (30 %) of Bunch berry are predicted to have hERG II (Human ether-a-go-go-related gene) inhibition activity. According to the docking analysis, lantic acid has the lowest atomic binding energy for all three target enzymes, hAchE (-6.23 kcal/mol), hCA-II (-4.46 kcal/mol), and hCES-I (-5.99 kcal/mol), respectively.
Conclusions: Thus the current find provides an advanced understanding the twenty selected ligands of Bunch berry as potent inhibitory agents of human acetylcholinesterase (hAchE), carbonic anhydrase II (hCA-II) and carboxylesterase 1 (hCES-1).

1. Introduction

Bunch berry (*Lantana camara*) is one among the well-known weed and is found throughout the world. It is an ornamental shrub, belongs to Verbenaceae family. Bunch berry has been classified into five different varieties based on their flower colour, they are i) orange; ii) pink; iii) pink edged red; iv) white and v) red (Kumar et al., 2016). Bunch berry has been utilized in traditional medicine for treating numerous inflammatory disorders including asthma, bronchitis, rheumatism and swellings. Moreover, Bunch berry has been utilized as an adjuvant/

Peer review under responsibility of King Saud University. Production and hosting by Elsevier.
* Corresponding author.
E-mail addresses: radhakrishnann.smc@saveetha.com, radhakrishnann.biochemistry@spiher.ac.in (N. Radhakrishnan), vchinnadurai@ksu.edu.sa (C. Veeramani), anewehy@ksu.edu.sa (A.S. El Newehy), malsaif@ksu.edu.sa (M.A. Alsaif), alnumair@ksu.edu.sa (K.S. Al-Numair).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.sjbs.2023.103847
Received 14 September 2023; Received in revised form 11 October 2023; Accepted 19 October 2023
Available online 20 October 2023

supplementary drug in treating a) bilious fevers, b) cancers, c) eye infections, d) chicken pox, e) eczema, f) measles, and g) high blood pressure. Furthermore, Bunch berry has been used in treating bone pain, malaria, mumps, palliate malaria, lymphadenitis, stomach-ache, and tuberculosis (El-Banna et al., 2022).

Bunch berries have been found to display a variety of biological properties, including anti-arthritic, anti-aspergillus (Nisha et al., 2014), anti-bacterial (Swamy et al., 2015), anti-cancer (Hublikar et al., 2023), cardioactive, anti-fertility, anti-filarial, hepato-protective, anti-hyperglycemic, anti-hyperlipidemic, anti-inflammatory, insecticidal, anti-microbial, anti-mutagenic, anxiolytic, nematicidial, anti-oxidant (Ruslin et al., 2022), anti-proliferative, anti-protozoal, anti-pyretic, anti-thrombin, anti-tumor, anti ulcerogenic, anti urolithiatic, anti-viral, and wound healing (Kumar et al., 2016). Bunch berry has been reported to inhibit the following enzyme activities like acetylcholinesterase (Nour et al., 2014), alpha amylase (Swamy and Sinniah, 2015), carboxylesterase (Bangou et al., 2011), cyclooxygenase-2 (El-Banna et al., 2022), inducible nitric oxide synthase (iNOS), glutathione-*S*-transferase (GST), 5-lipoxygenase (5-LOX), protein kinase C (Kumar et al., 2016) and xanthine oxidase (Mahdi-Pour et al., 2012). Consequently, past reports obligated us to conduct the current investigation on twenty chosen Bunch berry (*Lantana camara*) constituents which includes camaroside (flavone), campesterol (phytosterol), dipentene (terpene), epiloganin (iridoid glycoside), eucalyptol (monoterpene), ferulic acid (phenolic acid), geniposide (iridoid glycoside), hispidulin (flavonoid), icterogenin (triterpene), isonuomioside A (phenylethanoid glycoside), lamiridoside (iridoid glycoside), lantadene C (triterpene), lantic acid (triterpene), linaroside (flavonoid), pectolinarigenin (flavonoid), pectolinarin (flavonoid), theveside (iridoid glycoside), ursonic acid (triterpenoid), β-pinene (monoterpene) and β-sitosterol (phytosterol). These Bunch berry (*Lantana camara*) compounds were studied using the SwissDock approach in docking analyses with human acetylcholinesterase (hAchE), carbonic anhydrase II (hCA-II), and carboxylesterase 1 (hCES-1). Additionally, utilising the Molinspiration, Swiss ADME, pkCSM, and STITCH online servers, researchers looked into molecular physico-chemical, drug-likeness, ingesting, dispersing, metabolising, and excreting (ADME), toxicity and protein net interaction (STITCH) studies.

2. Methodology

2.1. Ligand preparation

Chemical structures of twenty ligands (Bunch berry) namely i) camaroside (CID no: 5315628); ii) campesterol (CID no: 173183); iii) dipentene (CID no: 22311); iv) epiloganin (CID no: 10548420); v) eucalyptol (CID no: 2758); vi) ferulic acid (CID no: 445858); vii) geniposide (CID no: 107848); viii) hispidulin (CID no: 5281628); ix) icterogenin (CID no: 45268134); x) isonuomioside (CID no: 45360354); xi) lamiridoside (CID no: 49775357); xii) lantadene C (CID no: 137381); xiii) lantic acid (CID no: 185503); xiv) linaroside (CID no: 11972339); xv) pectolinarigenin (CID no: 5320438); xvi) pectolinarin (CID no: 168849); xvii) theveside (CID no: 25085768); xviii) ursonic acid (CID no: 9890209); xix) β-pinene (CID no: 14896) and xx) β-sitosterol (CID no: 222284) were obtained from Pubchem database. And these 20 chosen ligands of Bunch berry were prepared by adopting the earlier method (Radhakrishnan et al., 2023). Thus, these prepared three dimensional structures were used for further study (SwissDock).

2.2. Molecular physicochemical and drug likeliness property analysis

Molinspiration free web server was used to analyse molecular physicochemical and drug likeliness properties of twenty selected ligands of Bunch berry (Radhakrishnan et al., 2023).

2.3. ADME analysis

Swiss ADME free web server was accustomed to analyse ADME (ingesting, dispersing, metabolising, and excreting) examination of twenty designated ligands of Bunch berry (Kumaraswamy et al., 2023).

2.4. Toxicity examination

Toxicity analysis was performed for twenty selected ligands of Bunch berry by the pkCSM free online server (Kumaraswamy et al., 2023).

2.5. Finding and making the target enzyme

Protein Data Bank (PDB) was used to download the three-dimensional (3D) structures of human acetylcholinesterase (hAchE-4EY6), human carbonic anhydrase II (hCA-II-1BCD), and human carboxylesterase 1 (hCES-1-2H7C), all of which have resolutions of 2.40, 1.90, and 2.00 A°, respectively. Using the Chimaera programme from UCSF, "A" chain of above said enzymes was processed separately by eliminating other chains, ligands, and water (H_2O) molecules that had been seen in crystallography (i.e., water without hydrogen bonds) (Kumaraswamy et al., 2023).

2.6. Docking analysis

A docking examination was conducted for twenty nominated ingredients of Bunch berry (*Lantana camara*) using the SwissDock online server (Grosdidier et al., 2011). The PyMOL software was employed for determining the binding site of each ligand's best-docked pose.

2.7. STITCH analysis (or) protein network interaction (PNI) determination

STITCH ("The search tool for interacting compounds") free-online server demonstrates the entire information [about the linkages between metabolic pathways, crystal structural information, possible binding affinities, and drug-target relationships] (Radhakrishnan et al., 2023). In the current investigation, STITCH web tool (Scklarczyk et al., 2016) was adopted for determining the interaction between 20 chosen ligands of Bunch berry (*Lantana camara*) and proteins of target organism (*Homo sapiens*).

3. Results

3.1. Molecular physicochemical analysis

The molecular physicochemical analysis of the current study has revealed that two ligands (isonuomioside and pectolinarin) predicted to exhibit three violations for Lipinski's rule of five (as shown in the Table 1). On the other hand eight ligands (dipentene, epiloganin, eucalyptol, ferulic acid, geniposide, hispidulin, pectolinarigenin and β-pinene) of Bunch berry have shown nil violations and have readily obeyed with the thumb rule of five (Lipinski's rule of five).

3.2. Analysis of drug-likeness attributes

Drug-likeness property analysis has shown that five ligands (namely dipentene, eucalyptol, ferulic acid, pectolinarin and β-pinene) of Bunch berry predicted to exhibit moderate bioactivity score against all the descriptors (as shown in the Table 2). On the other hand fifteen ligands (camaroside, campesterol, epiloganin, geniposide, hispidulin, icterogenin, isonuomioside, lamiridoside, lantadene C, lantic acid, linaroside, pectolinarigenin, theveside, ursonic acid and β-sitosterol) of Bunch berry had exhibited active (>0) to moderate bioactivity score.

Table 1
Molecular physicochemical evaluation of twenty (Bunch berry) ligands using the molinspiration free online server.

Ligands	Log A[i]	TPSA[ii]	Natoms[iii]	MW[iv]	nON[v]	nOHNH[vi]	Nviolations[vii]	Nrotb[viii]	Volume[ix]
	1.20	168.29	34	476.43	11	5	1	6	399.2
	8.30	20.23	29	400.69	1	1	1	5	439.7
	3.62	0.00	10	136.24	0	0	0	1	157.3
	−1.25	155.15	27	390.38	10	5	0	5	337.5
	2.72	9.23	11	154.25	1	0	0	0	166.7
	1.25	66.76	14	194.19	4	2	0	3	172.0
	−1.53	155.15	27	388.37	10	5	0	6	331.5
	2.48	100.13	22	300.27	6	3	0	2	249.6
	6.38	100.9	41	568.79	6	2	2	5	562.1
	−0.95	245.29	43	610.57	15	9	3	12	515.6
	−3.12	195.60	29	422.38	12	7	2	5	353.28
	7.74	80.67	40	554.81	5	1	2	5	560.0
	6.15	66.76	34	470.69	4	2	1	1	469.6
	1.00	168.29	34	476.43	11	5	1	6	399.2
	3.02	89.14	23	314.29	6	2	0	3	267.1
	0.30	227.21	44	622.58	15	7	3	8	523.1
	−3.09	186.37	27	390.34	11	7	2	5	321.7
	6.60	54.37	33	454.69	3	1	1	1	465.6
	3.33	0.00	10	136.24	0	0	0	0	152.37
	8.62	20.23	30	414.72	1	1	1	6	456.5

Note: Log A[i] - Octanol-Water partition coefficient; TPSA[ii] - Polar surface area; Natoms[iii] -Number of non-hydrogen atoms; MW[iv] - Molecular weight; nON[v] - Number of hydrogen bond acceptors [O and N atoms]; nOHNH[vi] -Number of hydrogen bond donors [OH and NH groups]; Nviolations[vii] - Number of Rule of 5 violations; Nrotb[viii] - Number of rotatable bonds; Volume[ix] - Molecular volume. 1) camaroside, 2) campesterol, 3) dipentene, 4) epiloganin, 5) eucalyptol, 6) ferulic acid, 7) geniposide, 8) hispidulin, 9) icterogenin, 10) isonuomioside A, 11) lamiridoside, 12) lantadene C, 13) lantic acid, 14) linaroside, 15) pectolinarigenin, 16) pectolinarin, 17) theveside, 18) ursonic acid, 19) β-pinene and 20) β-sitosterol.

3.3. ADME analysis

It has shown that five ligands (eucalyptol, ferulic acid, hispidulin, lantic acid and pectolinarigenin) of Bunch berry are predicted to possess high gastrointestinal absorption property (as shown in the Table 3). On the other hand, all fifteen ligands (camaroside, campesterol, dipentene, epiloganin, geniposide, icterogenin, isonuomioside, lamiridoside, lantadene C, linaroside, pectolinarin, theveside, ursonic acid, β-pinene and β-sitosterol) of Bunch berry predicted to exhibit low gastrointestinal absorption property. Four ligands (dipentene, eucalyptol, ferulic acid and β-pinene) have do not display any blood–brain barrier (BBB) permeable property. On other hand all sixteen ligands (camaroside, campesterol, epiloganin, geniposide, hispidulin, icterogenin, isonuomioside, lamiridoside, lantadene C, lantic acid, linaroside, pectolinarigenin, pectolinarin, theveside, ursonic acid and β-sitosterol) of Bunch berry predicted to possess blood–brain barrier (BBB) permeable nature. Nine ligands (camaroside, epiloganin, icterogenin, isonuomioside, lamiridoside, lantadene C, lantic acid, linaroside and pectolinarin) have predicted to possess plasma glycoprotein binding property. Two ligands (hispidulin and pectolinarigenin) of Bunch berry have predicted to exhibit cytochrome P450 (CYP1A2) inhibition activity. On the other hand, none of ligands have predicted to exhibit cytochrome P450 (CYP219) inhibition activity.

3.4. Toxicity analysis

It has shown that all the ligands of Bunch berry have does not exhibit any AMES and hERG I (ether-a-go-go-related molecular human gene) toxicity (as shown in the Table 4). In the present study, six ligands (camaroside, campesterol, isonuomioside, linaroside, pectolinarin and β-sitosterol) of Bunch berry have predicted to possess hERG II inhibition activity, thus six ligands fails to comply with the above said regulatory guideline (ICH S7B). One ligand (lantic acid) has predicted to exhibit hepatotoxicity nature. Similarly, two ligands (dipentene and eucalyptol) have predicted to exhibit skin sensitisation property.

3.5. The docking analysis

It has revealed that camaroside showed the highest binding energy (-9.34 kcal/mol) with the human acetylcholinesterase (hAchE) enzyme. In contrast, as indicated in Table 5, lantic acid has the lowest binding energy (-6.23 kcal/mol) with the human acetylcholinesterase (hAchE) enzyme.

The docking analysis observed that isonuomioside exhibited the maximum required energy (-9.72 kcal/mol) when combined with human carbonic anhydrase II (hCA-II) enzyme. As can be shown in Table 6, lantic acid has the lowest binding energy (-4.46 kcal/mol) when combined with human carbonic anhydrase II (hCA-II) enzyme.

Pectolinarin showed the greatest binding energy (-9.21 kcal/mol) with the human carboxylesterase 1 (hCES-1) enzyme, according to the docking analysis. The human carboxylesterase 1 (hCES-1) enzyme, however, had the least amount of binding energy (-5.99 kcal/mol) with lantic acid (Table 7). In the current investigation ursonic acid has shown ineffective docking with human carboxylesterase 1 (hCES-1) enzyme.

3.6. Three-dimensional (3D) structure

Fig. 1 represents the three-dimensional (3D) structure of A) camaroside with hAchE; B) isonuomioside A with hCA- II and C) pectolinarin with hCES −1.

Table 2
Drug-likeness property (or) bioactivity score investigation of twenty Bunch berry ligands using the molinspiration free online server.

Ligands	G PCR$^{\Diamond}$	Ion channel modulator (ICM)	Kinase inhibitor (KI)	Nuclear receptor ligand (NRL)	Protease inhibitor (PI)	Enzyme inhibitor (EI)
	0.01	−0.10	0.06	0.12	−0.08	0.35
	0.11	0.01	−0.48	0.71	0.01	0.50
	−0.91	−0.27	−2.01	−0.34	−1.38	−0.21
	0.28	0.10	−0.25	0.14	0.13	0.47
	−0.93	0.01	−1.60	−1.07	−0.90	−0.15
	−0.47	−0.30	−0.72	−0.14	−0.81	−0.12
	0.22	0.12	−0.30	0.08	0.14	0.45
	−0.07	−0.22	0.21	0.20	−0.33	0.17
	0.01	−0.49	−0.71	0.54	−0.01	0.43
	0.15	−0.32	−0.15	−0.13	0.22	0.22
	0.23	0.19	−0.19	0.04	0.13	0.47
	0.09	−0.38	−0.70	0.55	0.11	0.41
	0.18	0.01	−0.44	0.90	0.22	0.64
	0.01	−0.14	0.10	0.10	−0.12	0.32
	−0.09	−0.25	0.18	0.17	−0.29	0.14
	−0.13	−0.69	−0.24	−0.39	−0.13	−0.03
	0.42	0.26	−0.06	0.29	0.34	0.61
	0.18	−0.11	−0.68	0.84	0.13	0.61
	−0.53	−0.32	−1.45	−0.50	−0.80	−0.34
	0.14	0.04	−0.51	0.73	0.07	0.51

Note: GPCR$^{\Diamond}$- G Protein coupled receptors ligands, ICM-Ion channel modulator, KI-Kinase inhibitor, NRL-Nuclear receptor ligand, PI-Protease inhibitor, EI-Enzyme inhibitor, 1) camaroside, 2) campesterol, 3) dipentene, 4) epiloganin, 5) eucalyptol, 6) ferulic acid, 7) geniposide, 8) hispidulin, 9) icterogenin, 10) isonuomioside A, 11) lamiridoside, 12) lantadene C, 13) lantic acid, 14) linaroside, 15) pectolinarigenin, 16) pectolinarin, 17) theveside, 18) ursonic acid, 19) β-pinene and 20) β-sitosterol.

Table 3
ADME analysis of twenty Bunch berry ligands using the Swiss ADME free online server.

Ligands	GI [i] absorption	BBB [ii] permeability	P-gp [iii]	1A2 [iv]	2C19 [iv]	2C9 [iv]	2D6 [iv]	3A4 [iv]	Log K_p^v
	Low	No	Yes	No	No	No	No	Yes	−8.2
	Low	No	No	No	No	No	No	No	−2.5
	Low	Yes	No	No	No	Yes	No	No	−3.9
	Low	No	Yes	No	No	No	No	No	−9.7
	High	Yes	No	No	No	No	No	No	−5.3
	High	Yes	No	No	No	No	No	No	−6.4
	Low	No	No	No	No	No	No	No	−10.3
	High	No	No	Yes	No	No	Yes	Yes	−6.0
	Low	No	Yes	No	No	No	No	No	−4.7
	Low	No	Yes	No	No	No	No	No	−10.5
	Low	No	Yes	No	No	No	No	No	−11.4
	Low	No	Yes	No	No	No	No	No	−4.0
	High	No	Yes	No	No	No	No	No	−4.7
	Low	No	Yes	No	No	No	No	Yes	−8.38
	High	No	No	Yes	No	Yes	Yes	Yes	−5.9
	Low	No	Yes	No	No	No	No	No	−9.8
	Low	No	No	No	No	No	No	No	−11.0
	Low	No	No	No	No	No	No	No	−4.1
	Low	Yes	No	No	No	Yes	No	No	−4.2
	Low	No	No	No	No	No	No	No	−2.2

Note: GI^{i} –Gastrointestinal absorption, BBB^{ii} -Blood-brain barrier permeant, P-gp^{iii}-P-glycoprotein substrate, CYP $^{iv-}$ -Cytochrome P450 Inhibitors, Log K_p^v -Skin Permeation (cm/s),1) camaroside, 2) campesterol, 3) dipentene, 4) epiloganin, 5) eucalyptol, 6) ferulic acid, 7) geniposide, 8) hispidulin, 9) icterogenin, 10) isonuomioside A, 11) lamiridoside, 12) lantadene C, 13) lantic acid, 14) linaroside, 15) pectolinarigenin, 16) pectolinarin, 17) theveside, 18) ursonic acid, 19) β-pinene and 20) β-sitosterol.

3.7. STITCH analysis

Fig. 2 shown the ligands namely a) campesterol, b) dipentene, c) ferulic acid, d) geniposide, e) hispidulin and f) β-sitosterol have interacted with the human proteins using STITCH free online server.

4. Discussion

In India, Bunch berry (*Lantana camara*) leaves and twigs are commonly used as green mulch, and moreover leaf ash is rich source of manganese (Mn) and potassium (K) therefore it is utilized as manure for

Table 4
Toxicity analysis of twenty Bunch berry ligands using the pkCSM free online server.

Ligands	AT [i]	hERG-I [ii]	hERG-II [iii]	HT [iv]	SS [v]	ORAT (LD_{50}) [vi]	MT [vii]
1	No	No	Yes	No	No	2.76	3.66
2	No	No	Yes	No	No	2.08	−1.94
3	No	No	No	No	Yes	1.88	1.20
4	No	No	No	No	No	2.21	6.45
5	No	No	No	No	Yes	2.01	1.74
6	No	No	No	No	No	2.28	1.83
7	No	No	No	No	No	2.19	6.61
8	No	No	No	No	No	2.40	1.64
9	No	No	No	No	No	2.59	−1.11
10	No	No	Yes	No	No	2.57	5.17
11	No	No	No	No	No	2.24	8.78
12	No	No	No	No	No	2.40	−1.79
13	No	No	No	Yes	No	2.44	−0.44
14	No	No	Yes	No	No	2.64	4.22
15	No	No	No	No	No	2.01	0.48
16	No	No	Yes	No	No	2.52	5.35
17	No	No	No	No	No	2.16	7.58
18	No	No	No	No	No	2.26	−1.18
19	No	No	No	No	No	1.67	1.01
20	No	No	Yes	No	No	2.55	−1.80

Note: AT[i] -AMES toxicity, hERG I[ii]- Human ether-a-go-go-related gene inhibitor I, hERG II[iii]- Human ether-a-go-go-related gene inhibitor II, HT[iv]- Hepatotoxicity, SS[v]- Skin sensitisation, ORAT[vi]- Oral rat acute toxicity (Lethal dose LD_{50} in mol/kg), MT[vii]- Minnow toxicity (log mM), 1) camaroside, 2) campesterol, 3) dipentene, 4) epiloganin, 5) eucalyptol, 6) ferulic acid, 7) geniposide, 8) hispidulin, 9) icterogenin, 10) isonuomioside A, 11) lamiridoside, 12) lantadene C, 13) lantic acid, 14) linaroside, 15) pectolinarigenin, 16) pectolinarin, 17) theveside, 18) ursonic acid, 19) β-pinene and 20) β-sitosterol.

Cocos nucifera (coconut) trees. Moreover, in tropical countries including India the ripen fruits (blue-black berries) of *Lantana camara* are consumed by humans (Hussain et al., 2011). Furthermore, ripen fruits of *Lantana camara* along with fruits of *Opuntia ficus-indica* (cactus pear) are used in preparation of wine (Tsegay and Gebremedhin, 2019). Bunch berry (*Lantana camara*) has been used in several parts of the globe to treat numerous diseases. For instance i) in Central and South America, whole plant was utilized for treating asthma, colds, hypertension, and rheumatism; ii) in Ghana decoction of whole plant was used for treating bronchitis and stomach-ache in children's were treated by consuming powdered root of plant in milk and iii) in Asian countries including India, leaves of plant were used for treating cuts, intestinal worms, rheumatism and ulcers. Further, leaf decoction of plant was applied externally for treating leprosy and scabies (Hussain et al., 2011). Caffeic acid, coumarin, flavones, iridoid glycosides, monoterpenes, steroids and triterpenes derivatives have been reported previously from *Lantana* genus. Among these secondary metabolites of *Lantana* genus, flavones and triterpenes have been reported to possess the high quantities, and moreover shown to exhibit pharmacological activities (Hussain et al., 2011). Hence, the above- mentioned background engaged us to choose twenty phytochemicals of Bunch berry (*Lantana camara*) as ligands for the present study.

Acetylcholine (the substrate) is broken down into acetate and choline by the acetylcholinesterase (AchE), a unique enzyme. AchE has been used as drug target for managing neurodegenerative disorders (Roca et al., 2018). Thus, AchE was selected as one of target enzyme for the current in silico study. The hydration of carbon dioxide (CO_2) to bicarbonate (HCO_3) and proton is catalysed by a group of enzymes known as carbonic anhydrases (CA), which are members of the lyase family. CA has been used as drug target for managing diuretics, glaucoma, cancer and neurodegenerative disorders (O'Herin et al., 2023). Carboxylesterases are group of enzymes belongs to serine hydrolases family, which catalyze the hydrolysis of, amides, carbamates, esters and thioesters. Two human carboxylesterases (hCE1 and hCE2) plays a vital role in drug metabolism (Makhaeva et al., 2019). Therefore, hCE1 was

Table 5
Shows the swissdock method's investigation of the binding energies of 20 chosen (bunch berry) ligands with human acetylcholinesterase (ache).

S. no	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (A°)
1	Camaroside	9.34	Arg296	3.0 and 3.1
			Glu313	2.1
			His405	2.3
			Gln413	1.9
2	Campesterol	7.32	No interactions	–
3	Dipentene	6.41	No interactions	–
4	Epiloganin	8.50	Glu313	2.0
			His405	2.8
			Asn533	1.9
5	Eucalyptol	6.58	Asn186	3.4
6	Ferulic acid	7.21	Asp74	3.1
			Ser203	3.0 and 3.4
			Tyr337	3.2
7	Geniposide	8.41	Glu313	2.4
			Gln413	2.8 and 3.2
			Trp532	2.2
			Asn533	2.0
8	Hispidulin	7.24	Tyr72	3.1
			Thr75	3.0
			Leu76	3.2
			Ser293	2.9
			Arg296	3.3
9	Icterogenin	7.55	His322	2.4
10	Isonuomioside	9.05	Gln413	3.4
			Ala505	2.8
			Gln508	3.1
			Arg534	3.1, 3.3, 3.3 and 3.5
11	Lamiridoside	8.40	Glu431	2.0
			Tyr510	3.4
			Arg521	3.5
			Arg522	1.9 and 2.0
			Arg525	3.1, 3.3 and 3.4
12	Lantadene C	6.85	No interactions	–
13	Lantic acid	6.23	No interactions	–
14	Linaroside	8.91	Asn233	2.7 and 3.5
			Glu313	2.3
			His405	2.6
			Trp532	2.1
			Asn533	1.9
15	Pectolinarigenin	7.22	No interactions	–
16	Pectolinarin	8.18	Arg296	3.2 and 3.5
			Leu540	3.3
17	Theveside	8.56	Glu313	1.9
			Pro368	1.9 and 3.4
			His405	2.5 and 3.2
			Gln413	2.1
18	Ursonic acid	Failed ◊		
19	β-pinene	6.25	No interactions	–
20	β-sitosterol	7.68	No interactions	–

Note: Failed ◊- Failed to dock.

selected for the current in silico analysis as one of the target enzymes.

Previous analysis study, it is crucial to recognize the molecular physico-chemical, drug- likeness, ADME, and toxicity nature of selected Bunch berry ligands to avoid drug failure as well as save drug development cost (Radhakrishnan et al., 2023). The molecular physico-chemical analysis of the current study has demonstrated that two (10 %) ligands (isonuomioside and pectolinarin) expected to exhibit three violations for Lipinski's rule of five (as shown in Table 1), which has been confirmed. The eight (40 %) ligands of the Bunch berry, on the other hand, (dipentene, epiloganin, eucalyptol, ferulic acid, geniposide, hispidulin, pectolinarigenin, and β -pinene) have exhibited no violations and have readily complied with the thumb rule of five.

Drug-likeness property /bioactivity score investigation has shown that five (25 %) ligands (namely dipentene, eucalyptol, ferulic acid, pectolinarin and β-pinene) of Bunch berry predicted to exhibit moderate

Table 6
The Swissdock approach binding energy analysis of 20 chosen (Bunch berry) ligands with human carbonic anhydrase II (hCA-II).

S. no	Ligands	Swissdock (-kcal/mol)	Interactions of amino acids residues	Bond distance (A)
1	Camaroside	8.13	His64	3.3
			Gln92	3.0
			His94	2.1
			His96	3.1
			Thr199	3.0 and 3.3
			Thr200	3.1
2	Campesterol	7.18	No interactions	–
3	Dipentene	6.03	No interactions	–
4	Epiloganin	7.57	Trp5	3.3
			Gln92	3.4
			Thr200	3.4
			Pro201	2.3
5	Eucalyptol	5.90	No interactions	–
6	Ferulic acid	7.92	Asn62	3.2
			Glu69	2.0 and 2.1
			Gln92	3.3
			Thr200	3.2
7	Geniposide	7.81	Asn62	3.1
			Glu69	2.1 and 2.2
8	Hispidulin	7.24	His119	2.4
9	Icterogenin	5.81	His3	3.3
			His10	3.4
			Phe231	3.4
			Glu236	2.2
			Glu239	2.7
10	Isonuomioside	9.72	His4	2.1
			His64	3.0
			Gln92	3.2
			Lys170	3.3
			Thr199	2.9 and 3.0
			Thr200	3.0
11	Lamiridoside	8.85	Asn62	3.2 and 3.3
			Glu69	2.0 and 2.5
			Gln92	3.3 and 3.3
			Thr200	2.1 and 3.3
12	Lantadene C	6.17	No interactions	–
13	Lantic acid	4.46	Asn11	3.4
			Glu239	2.9
14	Linaroside	7.82	No interactions	–
15	Pectolinarigenin	7.20	Asn67	3.2 and 3.3
			Thr200	3.5
16	Pectolinarin	8.71	Asn62	3.0
			Gln92	3.2
17	Theveside	8.09	His64	3.4
			His94	2.0
			His96	3.1
			Thr199	3.0 and 3.5
			Thr200	3.1
18	Ursonic acid	7.32	Trp5	3.5
			Gln92	3.1
19	β-pinene	6.04	No interactions	–
20	β-sitosterol	7.61	No interactions	–

Table 7
Shows the swissdock method's investigation of the binding energies of 20 chosen (bunch berry) ligands with human carboxylesterase 1 (hces-1).

S. no	Ligand	Swissdock (-kcal/mol)	Interactions of amino acids residues	Bond distance (A)
1	Camaroside	8.17	No interactions	–
2	Campesterol	8.39	No interactions	–
3	Dipentene	6.81	No interactions	–
4	Epiloganin	7.52	Cys1390	2.0 and 2.1
			Phe1551	2.2
5	Eucalyptol	6.69	No interactions	–
6	Ferulic acid	6.66	No interactions	–
7	Geniposide	8.69	Lys1257	3.1
			Lys1258	2.4
			Asp1260	2.6
			Ser1315	2.3
			Gln1316	3.3
8	Hispidulin	7.27	Phe1055	1.9
9	Icterogenin	6.67	Val1256	3.1
			Asp1260	1.9
10	Isonuomioside	8.78	Arg1313	2.2
			Cys1390	2.3 and 2.3
			Thr1548	3.5
11	Lamiridoside	8.21	His1030	2.0 and 3.5
			Phe1055	1.9 and 2.1
			Ala1071	3.4
			Asp1203	1.9
12	Lantadene C	7.20	Lys1414	3.2 and 3.4
13	Lantic acid	5.99	Lys1036	3.3
			Tyr1083	2.2 and 3.4
			Arg1104	3.2
14	Linaroside	7.99	Gln1267	1.9 and 2.0
			Glu1314	2.4
15	Pectolinarigenin	7.37	No interactions	–
16	Pectolinarin	9.21	Ser1253	3.2
			Lys1257	3.4
			Val1424	1.9
17	Theveside	8.33	Lys1257	3.2
			Gln1267	1.9
			Gln1316	3.5
			Tyr1386	3.3
18	Ursonic acid	Failed◊		
19	β-pinene	6.85	No interactions	–
20	β-sitosterol	7.38	No interactions	–

Note: Failed ◊- Failed to dock.

bioactivity score against all the descriptors (as shown in the Table 2). On the other hand, fifteen (75 %) ligands (camaroside, campesterol, epiloganin, geniposide, hispidulin, icterogenin, isonuomioside, lamiridoside, lantadene C, lantic acid, linaroside, pectolinarigenin, theveside, ursonic acid and β-sitosterol) of Bunch berry had exhibited active (>0) to moderate bioactivity score.

ADME analysis has shown that five (25 %) ligands (eucalyptol, ferulic acid, hispidulin, lantic acid and pectolinarigenin) of Bunch berry predicted to possess high GI absorption property (as shown in the Table 3). On the other hand, all fifteen (75 %) ligands (camaroside, campesterol, dipentene, epiloganin, geniposide, icterogenin, isonuomioside, lamiridoside, lantadene C, linaroside, pectolinarin, theveside, ursonic acid, β-pinene and β-sitosterol) of Bunch berry predicted to show low GI absorption property. Four (20 %) ligands (dipentene, eucalyptol, ferulic acid and β-pinene) have do not exhibit any BBB permeable property, whereas all sixteen (80 %) ligands (camaroside, campesterol, epiloganin, geniposide, hispidulin, icterogenin, isonuomioside, lamiridoside, lantadene C, lantic acid, linaroside, pectolinarigenin, pectolinarin, theveside, ursonic acid and β-sitosterol) of Bunch berry predicted to possess BBB permeable nature. Nine (45 %) ligands (camaroside, epiloganin, icterogenin, isonuomioside, lamiridoside, lantadene C, lantic acid, linaroside and pectolinarin) have predicted to possess plasma glycoprotein binding property. Two (10 %) ligands (hispidulin and pectolinarigenin) of Bunch berry have predicted to exhibit CYP1A2 inhibition activity. On the other hand, none of ligands have predicted to exhibit any CYP219 inhibition activity.

According to regulatory guidelines (ICH S7B) every new medication in development should examine for belongings on the hERG channel (human ether-a-go-go-related gene) before to clinical trials (Frolov et al., 2011). In the present study, six (30 %) ligands (camaroside, campesterol, isonuomioside, linaroside, pectolinarin and β-sitosterol) of Bunch berry have failed to comply with the above said regulatory guideline (ICH S7B). Moreover, one ligand (lantic acid) has predicted to exhibit hepatotoxicity nature. Furthermore, two (10 %) ligands (dipentene and eucalyptol) have predicted to exhibit skin sensitisation property.

The docking analysis revealed that camaroside (flavone) exhibited the maximum binding energy (-9.34 kcal/mol) with the human acetylcholinesterase (hAchE) enzyme. In contrast, as indicated in Table 5, lantic acid (triterpene) had the lowest binding energy (-6.23 kcal/mol)

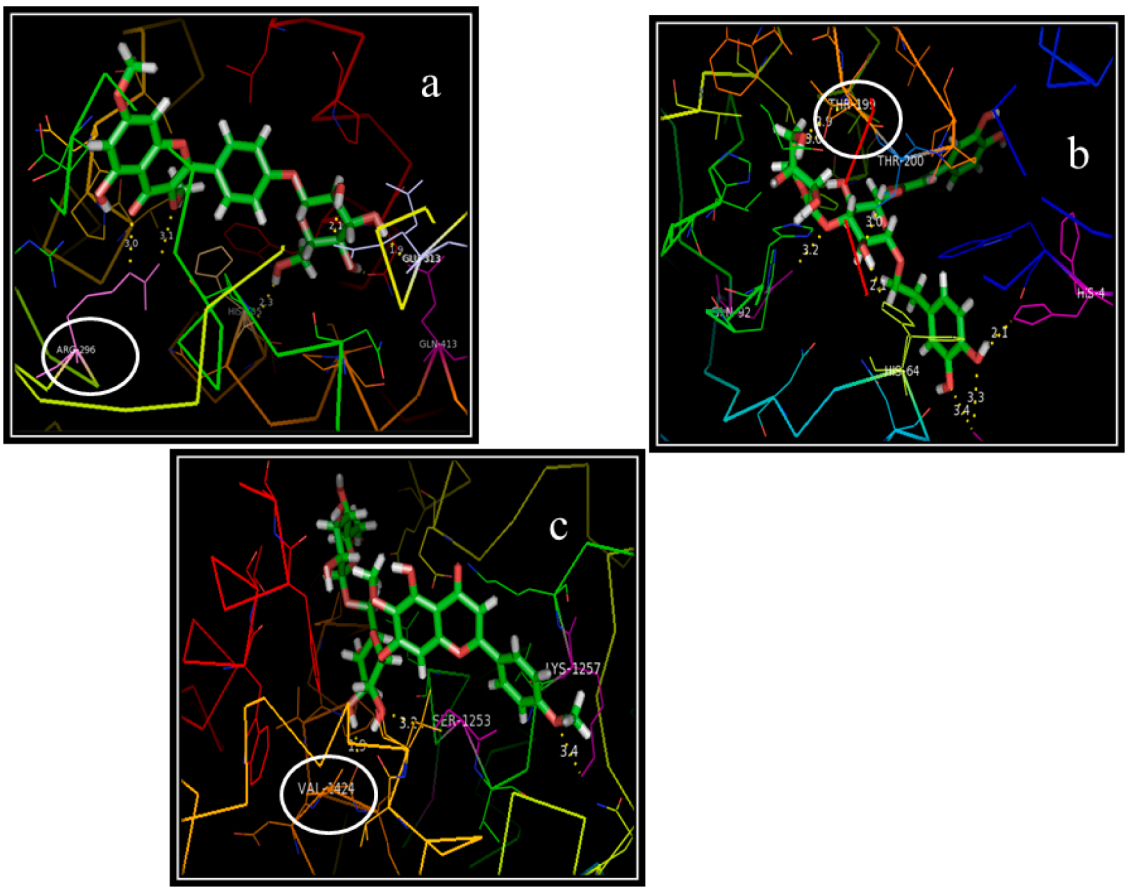

Fig. 1. Represents the three-dimensional (3d) structure of a) camaroside with hache; b) isonuomioside a with hca ii and c) pectolinarin with hCES 1.

with the human acetylcholinesterase (hAchE) enzyme. The binding energy results shown in descending order: camaroside (-9.34 kcal/mol), < isonuomioside (-9.05 kcal/mol), < linaroside (-8.91 kcal/mol), < theveside (-8.56 kcal/mol), < epiloganin (-8.50 kcal/mol), < geniposide (-8.41 kcal/mol), < lamiridoside (-8.40 kcal/mol), < pectolinarin (-8.18 kcal/mol), < β-sitosterol (-7.68 kcal/mol), < icterogenin (-7.55 kcal/mol), < campesterol (-7.32 kcal/mol), < hispidulin (-7.24 kcal/mol), < pectolinarigenin (-7.22 kcal/mol), < ferulic acid (-7.21 kcal/mol), < lantadene C (-6.85 kcal/mol), < eucalyptol (-6.58 kcal/mol), < dipentene (-6.41 kcal/mol), < β-pinene (-6.25 kcal/mol) and < lantic acid (-6.23 kcal/mol).

As indicated in Table 5, five (25 %) ligands [camaroside (Fig. 1a), epiloganin, geniposide, linaroside, and theveside] have interacted with the Glu313 amino acid (AA) residue of the human acetylcholinesterase (AchE) enzyme. The present investigation was in strong agreement with the earlier study, which had identified the amino acid Glu313 as an allosteric (site 2) residue of human acetylcholinesterase (Roca et al., 2018). Four (20 %) ligands (camaroside, epiloganin, linaroside and theveside) displayed interaction with His405 amino acid (AA) residue of human acetylcholinesterase (AchE). The new finding was well correlated with the preceding study, which focused on the amino acid His405 has been shown as one of allosteric (site 2) residue of human acetylcholinesterase (Roca et al., 2018). Four (20 %) ligands (camaroside, geniposide, isonuomioside and theveside) displayed interaction with Gln413 amino acid (AA) residue of human acetylcholinesterase (AchE). Where Gln413 amino acid has been shown as one of allosteric (site 2) residue of human acetylcholinesterase (Roca et al., 2018). Three (15 %) ligands (epiloganin, geniposide and linaroside) displayed interaction with Asn533 amino acid (AA) residue of human acetylcholinesterase (AchE). Asn533 amino acid has been exposed as one of allosteric (site 2) residue of human acetylcholinesterase (Roca et al., 2018). Interesting, two ligands (β-pinene and β-sitosterol) does not show any interactions with that of human acetylcholinesterase (AchE) enzyme. Crude Bunch berry (*Lantana camara*) has been reported to inhibit the AchE activity, in dose response manner with 50 % inhibition concentration at (IC_{50} value) 47 and 56 μg/ml (root and leaf extract) respectively (Nour et al., 2014).

The docking analysis observed that isonuomioside (phenylethanoid glycoside) demonstrated the most vigour (-9.72 kcal/mol) when combined with human carbonic anhydrase II (hCA-II) enzyme. As represented in Table 6, lantic acid (triterpene) possesses the least binding energy (-4.46 kcal/mol) when combined with human carbonic anhydrase II (hCA-II) enzyme. The binding energy results showed the descending order: isonuomioside (-9.72 kcal/mol), < lamiridoside (-8.85 kcal/mol), < pectolinarin (-8.71 kcal/mol), < camaroside (-8.13 kcal/mol), < theveside (-8.09 kcal/mol), < ferulic acid (-7.92 kcal/mol), < linaroside (-7.82 kcal/mol), < geniposide (-7.81 kcal/mol), < β-sitosterol (-7.61 kcal/mol), < epiloganin (-7.57 kcal/mol), < ursonic acid (-7.32 kcal/mol), < hispidulin (-7.24 kcal/mol), < pectolinarigenin (-7.20 kcal/mol), < campesterol (-7.18 kcal/mol), < lantadene C (-6.17 kcal/mol), < β-pinene (-6.04 kcal/mol), < dipentene (-6.03 kcal/mol), < eucalyptol (-5.90 kcal/mol), < icterogenin (-5.81 kcal/mol) and < lantic acid (-4.46 kcal/mol).

Thr200 amino acid (AA) residue of the human carbonic anhydrase II (hCA-II) enzyme was in interaction with seven (35 %) ligands (camaroside, epiloganin, ferulic acid, isonuomioside, lamiridoside, pectolinarigenin, and theveside), as indicated in Table 6. The present investigation was consistent with earlier research, which revealed that the Thr200 amino acid is located closest to the cavity entrance of human carbonic anhydrase II (Krishnamurthy et al., 2008). Seven (35 %) ligands have been shown to interrelate with the Gln92 amino acid (AA) residue of human carbonic anhydrase II (hCA-II), including camaroside, epiloganin, ferulic acid, isonuomioside [Fig. 1b], lamiridoside,

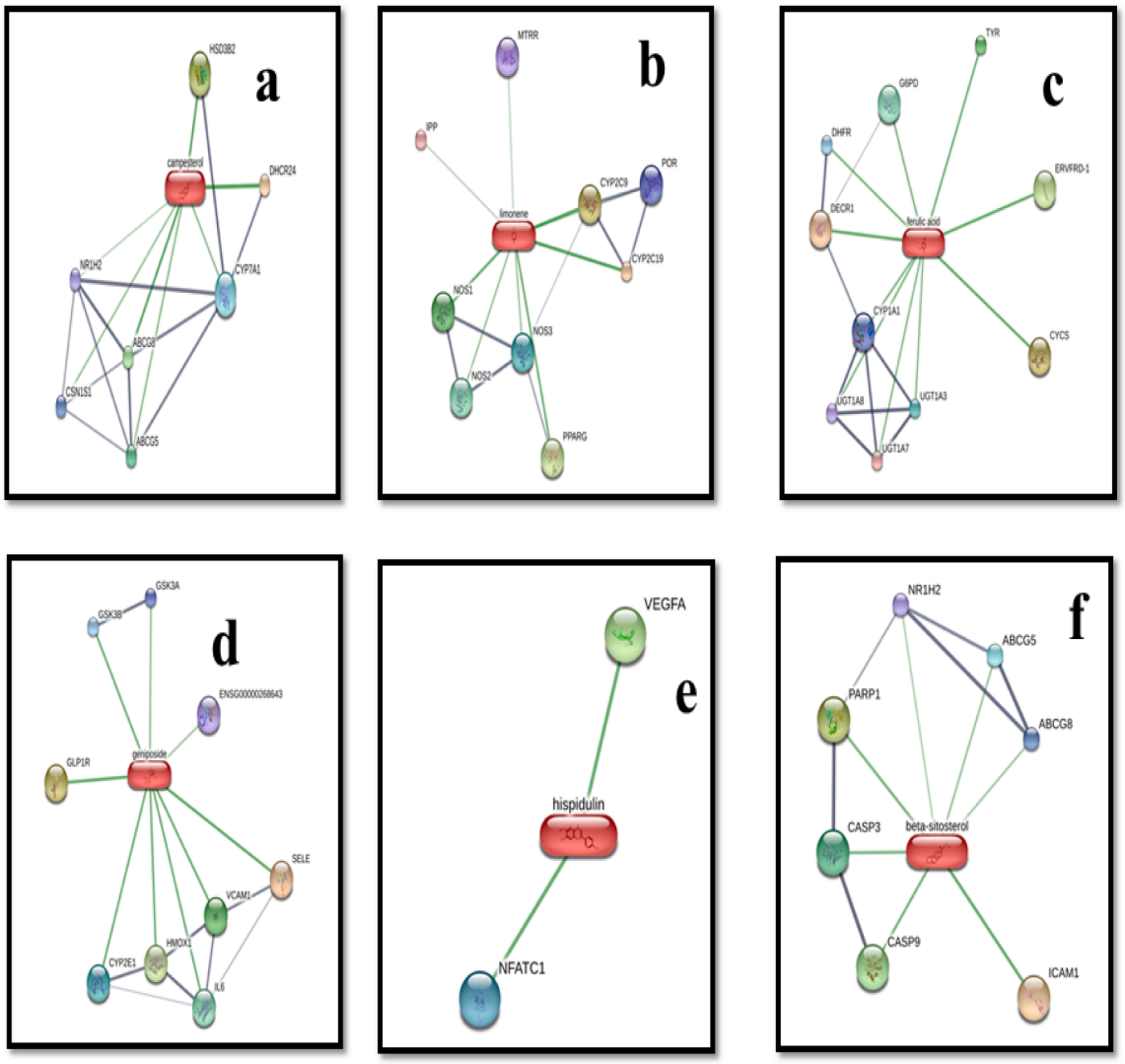

Fig. 2. Shown the ligand-protein of a) campesterol, b) dipentene, c) ferulic acid, d) geniposide, e) hispidulin and f) β-sitosterol have interacted with the human proteins using stitch free online server.

pectolinarin, and ursonic acid. The current finding was well-concordant with an earlier work in which the amino acid Gln92 was identified as a residue in the active region of human carbonic anhydrase II (Krishnamurthy et al., 2008). The human carbonic anhydrase II (hCA-II) Asn62 amino acid residue interacted with four (20 %) ligands: ferulic acid, geniposide, lamiridoside, and pectolinarin. Asn62 amino acid was identified in a prior study as one of the active site residues of human carbonic anhydrase II (Krishnamurthy et al., 2008). The human carbonic anhydrase II (hCA-II) His64 amino acid (AA) residue interacted with three (15 %) ligands (camaroside, isonuomioside, and theveside). His64 amino acid was important for the proton transport process in human carbonic anhydrase II (Krishnamurthy et al., 2008). It's interesting to show that human carbonic anhydrase II (hCA-II) does not interact with two ligands (β-pinene and β-sitosterol).

Pectolinarin (flavonoid) established the highest binding energy (-9.21 kcal/mol) with the human carboxylesterase 1 (hCES-1) enzyme, with regard to docking analysis. The human carboxylesterase 1 (hCES-1) enzyme, however, had the least amount of binding energy (-5.99 kcal/mol) with lantic acid (Table 7).

In the current investigation ursonic acid (triterpenoid) has shown ineffective docking with human carboxylesterase 1 (hCES-1) enzyme. This finding was in par with the earlier study, where taxol has failed to dock due to unfavourable binding nature (Castro et al., 2009). The binding energy results showed the descending order: pectolinarin (–9.21 kcal/mol), < isonuomioside (-8.78 kcal/mol), < geniposide (-8.69 kcal/mol), < campesterol (-8.39 kcal/mol), < theveside (-8.33 kcal/mol), < lamiridoside (-8.21 kcal/mol), <camaroside (-8.17 kcal/mol), < linaroside (-7.99 kcal/mol), < epiloganin (-7.52 kcal/mol), < β-sitosterol (-7.38 kcal/mol), < pectolinarigenin (-7.37 kcal/mol), < hispidulin (-7.27 kcal/mol), < lantadene C (-7.20 kcal/mol), < β-pinene (-6.85 kcal/mol), < dipentene (-6.81 kcal/mol), < eucalyptol (-6.69 kcal/mol), < icterogenin (-6.67 kcal/mol), < ferulic acid (-6.66 kcal/mol) and < lantic acid (-5.99 kcal/mol).

Three (15 %) ligands (geniposide, pectolinarin [Fig. 1c] and theveside) have showed interaction with Lys1257 amino acid (AA) residue of human carboxylesterase 1 (hCES-1). Two ligands (hispidulin and lamiridoside) have presented collaboration with Phe1055 amino acid (AA) residue of human carboxylesterase 1 (hCES-1) enzyme as shown in the Table 7. In the current study none of selected ligands of Bunch berry found to interact with active sites (Ser221 and His468) of human carboxylesterase 1 (hCES-1), this finding was in par with earlier report (Makhaeva et al., 2019). Interesting, eight (40 %) ligands (camaroside, campesterol, dipentene, eucalyptol, ferulic acid, pectolinarigenin β-pinene and β-sitosterol) does not show any interactions with that of human carboxylesterase 1 (hCES-1). Crude Bunch berry (*Lantana camara*) extract has been reported to inhibit the porcine liver CES

activity with IC_{50} value < 100 μg/ml (Bangou et al., 2011). Five phytochemicals (bavachinin, coryfolin, corylin, oleanolic acid and ursolic acid) have allegedly inhibited to human carboxylesterase 1 (hCES-1) activity (Sun et al., 2016; Zou et al., 2017).

The free web server "Search Tool for Interacting Compounds" [STITCH] displays all information regarding the relationships between drugs and their targets as well as the interactions between metabolic pathways, crystal structures, probable binding affinities, and interactions between drugs and their targets (Radhakrishnan et al., 2023). In the current investigation, STITCH web tool (Scklarczyk et al., 2016) was utilized for determining the interaction between 20 selected ligands of bunch berry *(Lantana camara*) and proteins of target organism (human). In this study, STITCH analysis shows that six (30 %) ligands of Bunch berry (*Lnntana camara*) namely campesterol, dipentene, ferulic acid, geniposide, hispidulin, and β-sitosterol have exhibited interactions with the *homo sapiens/* human proteins (Fig. 2 a-f). Interestingly, in the current investigation we observed that hispidulin (Fig. 2e) had displayed the least interactions with the *homo sapiens* proteins.

5. Conclusion

The current study showed that all twenty ligands of Bunch berry have dock effectively with human carbonic anhydrase II (hCA-II) enzyme. Only ligand (Ursonic acid) found to be ineffective in both docking and binding with both the targeted enzymes [human acetylcholinesterase (hAchE) and carboxylesterase (hCES-1)]. Interesting, lantic acid (triterpene) had exhibited the least atomic binding energy for all the three target enzymes (hAchE, hCA-II and hCES-1). Thus, the findings of this current study have shown good insight of these 20 ligands of Bunch berry as potential suppresser against hAchE, hCA-II and hCES-1 concerning the treatments of diuretics, glaucoma, cancer, and neurodegenerative disorders.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like thank authorities of Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to University), Chennai for providing us support to conduct the study.

The authors express their sincere appreciation to the Researchers Supporting Project Number (RSPD2023R1102), King Saud University, Riyadh, Saudi Arabia.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2023.103847.

References

Bangou, M.J., Kiendrebeogo, M., Compaoré, M., Coulibaly, A.Y., Meda, N.T.R., Abarca, N.A., Zeba, B., Millogo-Rasolodimby, J., Nacoulma, O.G., 2011. Enzyme inhibition effect and polyphenolic content of medicinal plant extracts from Burkina Faso. J. Biol. Sci. 11 (1), 31–38.

Castro, J.S., Trzaskowski, B., Deymier, P.A., Bucay, J., Adamowicz, L., Hoying, J.B., 2009. Binding affinity of fluorochromes and fluorescent proteins to Taxol™ crystals. Mater. Sci. Eng. C 29 (5), 1609–1615.

El-Banna, A.A., Darwish, R.S., Ghareeb, D.A., Yassin, A.M., Abdulmalek, S.A., Dawood, H.M., 2022. Metabolic profiling of *Lantana camara* L. using UPLC-MS/MS and revealing its inflammation-related targets using network pharmacology-based and molecular docking analyses. Sci. Rep. 12 (1), 14828.

Frolov, R.V., Ignatova, I.I., Singh, S., 2011. Inhibition of HERG potassium channels by celecoxib and its mechanism. PLoS One 6 (10), e26344.

Grosdidier, A., Zoete, V., Michielin, O., 2011. SwissDock, a protein-small molecule docking web service based on EADock DSS. Nucleic Acids Res. 39 (suppl_2), W270–W277.

Hublikar, L.V., Ganachari, S.V., Patil, V.B., Nandi, S., Honnad, A., 2023. Anticancer potential of biologically synthesized silver nanoparticles using *Lantana camara* leaf extract. Prog. Biomater. 12 (2), 155–169.

Hussain, H., Hussain, J., Al-Harrasi, A., Shinwari, Z.K., 2011. Chemistry of some species genus Lantana. Pak. J. Bot. 43 (3), 51–62.

Krishnamurthy, V.M., Kaufman, G.K., Urbach, A.R., Gitlin, I., Gudiksen, K.L., Weibel, D. B., Whitesides, G.M., 2008. Carbonic anhydrase as a model for biophysical and physical-organic studies of proteins and protein− ligand binding. Chem. Rev. 108 (3), 946–1051.

Kumar, R., Katiyar, R., Kumar, S., Kumar, T., Singh, V., 2016. *Lantana camara*: An alien weed, its impact on animal health and strategies to control. J. Exp. Biol. 4, 3S.

Kumaraswamy, S., Arumugam, G., Pandurangan, A.K., Prabhakaran, V.S., Narayanaswamy, R., 2023. Molecular docking analysis of organic acids (OA) from honey as modulators of human ferritin, transferrin, and hepcidin. J. Microbiol. Biotechnol. Food Sci. 12 (5), e5743–e.

Mahdi-Pour, B., Jothy, S.L., Latha, L.Y., Chen, Y., Sasidharan, S., 2012. Antioxidant activity of methanol extracts of different parts of *Lantana camara*. Asian Pac. J. Trop. Biomed. 2 (12), 960–965.

Makhaeva, G.F., Elkina, N.A., Shchegolkov, E.V., Boltneva, N.P., Lushchekina, S.V., Serebryakova, O.G., Rudakova, E.V., Kovaleva, N.V., Radchenko, E.V., Palyulin, V. A., Burgart, Y.V., 2019. Synthesis, molecular docking, and biological evaluation of 3-oxo-2-tolylhydrazinylidene-4, 4, 4-trifluorobutanoates bearing higher and natural alcohol moieties as new selective carboxylesterase inhibitors. Bioorg. Chem. 91, 103097.

Nisha, H.B., Iswarya, S., Kavitha, V., Mandal, A.B., Gnanamani, A., 2014. Anti-aspergillus activity of *Lantana camara* Linn. Int. J. Pharm. Sci. Res. 5 (10), 4320–4324.

Nour, A.H., Khan, M., Sulaiman, A.Z., Batool, T., Nour, A.H., Khan, M.M., Kormin, F., 2014. In vitro anti-acetylcholinesterase and antioxidant activity of selected Malaysian plants. Asian J. Pharm. Clin. Res. 7 (3), 93–97.

O'Herin, C.B., Moriuchi, Y.W., Bemis, T.A., Kohlbrand, A.J., Burkart, M.D., Cohen, S.M., 2023. Development of Human Carbonic Anhydrase II Heterobifunctional Degraders. J. Med. Chem. 66 (4), 2789–2803.

Radhakrishnan, N., Prabhakaran, V.S., Wadaan, M.A., Baabbad, A., Vinayagam, R., Kang, S.G., 2023. STITCH, Physicochemical, ADMET, and In Silico Analysis of Selected Mikania Constituents as Anti-Inflammatory Agents. Processes 11 (6), 1722.

Roca, C., Requena, C., Sebastián-Pérez, V., Malhotra, S., Radoux, C., Pérez, C., Martinez, A., Antonio Paez, J., Blundell, T.L., Campillo, N.E., 2018. Identification of new allosteric sites and modulators of AChE through computational and experimental tools. J. Enzyme Inhib. Med. Chem. 33 (1), 1034–1047.

Ruslin, Y., Rahma, N.A., Irnawati, Rohman, A., 2022. UPLC MS/MS profile and antioxidant activities from nonpolar fraction of patiwala (Lantana camara) leaves extract. Separations 9 (3), 75.

Sun, D.X., Ge, G.B., Dong, P.P., Cao, Y.F., Fu, Z.W., Ran, R.X., Wu, X., Zhang, Y.Y., Hua, H.M., Zhao, Z., Fang, Z.Z., 2016. Inhibition behavior of fructus psoraleae's ingredients towards human carboxylesterase 1 (hCES1). Xenobiotica 46 (6), 503–510.

Swamy, M.K., Sinniah, U.R., 2015. Phytochemical profile and in vitro α-amylase inhibitory potential of different solvent extracts of *Lantana camara*. Bangladesh Journal of Pharmacology 10 (4), 962–963.

Swamy, M.K., Sinniah, U.R., Akhtar, M., 2015. In vitro pharmacological activities and GC-MS analysis of different solvent extracts of *Lantana camara* leaves collected from tropical region of Malaysia. Evid. Based Complement. Alternat. Med. 2015, 506713.

Szklarczyk, D., Santos, A., Von Mering, C., Jensen, L.J., Bork, P., Kuhn, M., 2016. STITCH 5: augmenting protein-chemical interaction networks with tissue and affinity data. Nucleic Acids Res. 44, D380–D384.

Tsegay, Z.T., Gebremedhin, K.M., 2019. Physicochemical and sensory properties of wine produced from blended cactus pear (Opuntia ficus-indica) and Lantana camara (L. camara) fruits. J. Food Qual. 2019, 1–11.

Zou, L.W., Dou, T.Y., Wang, P., Lei, W., Weng, Z.M., Hou, J., Wang, D.D., Fan, Y.M., Zhang, W.D., Ge, G.B., Yang, L., 2017. Structure-activity relationships of pentacyclic triterpenoids as potent and selective inhibitors against human carboxylesterase 1. Front. Pharmacol. 8, 435.