Original Article

Docking and ADMET Study of Ar-Turmerone: Emerging Scaffold for Acetylcholine Esterase Inhibition and Antidiabetic Target

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Citation M. Yusuf, S. Pal, M. Shahid, M. Asif, S. Ahmad Khan, R. Tyagi. **Docking and ADMET Study of Ar-Turmerone: Emerging Scaffold for Acetylcholine Esterase Inhibition and Antidiabetic Target.** *J. Appl. Organomet. Chem.*, **2023**, *3*(1), 52-60.

https://doi.org/10.22034/JAOC.2023.384164.1070

Article info:
Received: 1 February 2023
Accepted: 23 February 2023
Available Online: 01 March 2023
ID: JAOC-2302-1070
Checked for Plagiarism: Yes
Language Editor checked: Yes

Keywords:
In-Silico study, Ar-turmerone, Alzheimer's disease, Acetylcholine esterase, Antidiabetic target

ABSTRACT

In the present scenario of eco-preservation and eco-safe utilization, researchers globally have been attracted to the utilization of raw and sustainable products having significant therapeutic potential that allow safety, modality, and biological activeness with environmental compatibility. Ar-turmerone has various pharmacological actions, including antidepressant, antiepileptic, anti-dermatophyte, antivenom, anticancer, antiplatelet activity, etc. In the present work, we investigated Ar-Turmerone (Ar-Tume), one of the chief phytoconstituents present in Curcuma longa for human anticholinesterase (AChE) inhibitor (4PQE) and human salivary alpha-Amylase dimer (1XV8) hydrolase inhibitor as a natural product-based emerging scaffold. Our study reveals that the selected compound Ar-Tume showed remarked biological, ADMET profiling, and superior docking scores/negative binding energies (-7.9 against 4PQE and -6.7 against 1XV8) concerning the reference drugs, which attributed to the strong hydrogen-bonding interactions both towards both anti-Alzheimers and antidiabetic capabilities.

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Introduction

In the 21st century, computer-aided drug design (CADD) enables a better understanding of synthetic protocols that provide the opportunity to transform drug development towards developing novel drugs with superior clinical properties. In this regard, many repurposed drugs have been developed using computational approaches and approved by FDA at a faster quicker approach to the clinical trials to treat several diseases such as inflammation, hypertension, obesity, type-2 diabetes, and Alzheimer's disease (**Figure 1**) [1, 2]. The CADD approach further helps assess whether natural products/phytoconstituents cope with biological activity [3]. Natural products contain a range of phytochemical classes such as indole, quinolizidine, isoquinoline, stilbenes, piperidine, phenolics, flavonoids, and terpenoids [4-6], which have profound effects to exhibit excellent eco-friendly therapeutic potential along with better biodegradation with high environmental compatibility possessing the excellent bioactive functionalities owing to their core moieties [7].

Turmeric (*Curcuma longa*), often used as a spice and affects the nature, color, and taste of foods, under the family *Zingiberaceae*, is commonly called turmeric or Haldi, typically cultivated and propagated in the tropical part of Asia, including India, China, Thailand, Iran, Malaysia, etc. The chief medicinally important part is its rhizome which contains curcuminoids, phenolics, aromatic quinone, quinines, and other bioactive compounds. The extract of Haldi is traditionally known for its therapeutic and biological engagements, for example, antioxidant, cardiovascular diseases, diabetic, immune-boosting, anti-inflammatory, anticancer, etc. Turmerones, the principal sesquiterpenes occurred naturally in turmeric, are α-turmerone, aromatic-turmerone, and β-turmerone, out of which Ar-turmerone is a major bioactive phytoconstituent [8]. Ar-turmerone is one of the main compounds contained in turmeric essential oil. Ar-turmerone also has diverse biological activities, as well as curcumin. Hucklenbroich *et al.* reported that Ar-turmerone inhibited microglia activation indicating its effectiveness in treating neurodegenerative diseases [9]. In a previous study, we found that curcuminoids and other turmeric constituents had significant *in silico* ADME and COX-2 inhibitory activity [10]. Ar-turmerone has powerful antivenom action against snake bites [11]. Likewise, Ar-turmerone has anti-inflammatory, anti-aging, anti-plasmodial, and neuroprotective activities [12-14]. In addition, with a certain dose, ar-turmerone has biological activities such as antiepileptic, antidepressant, anti-dermatophyte, anticancer, and antiplatelet

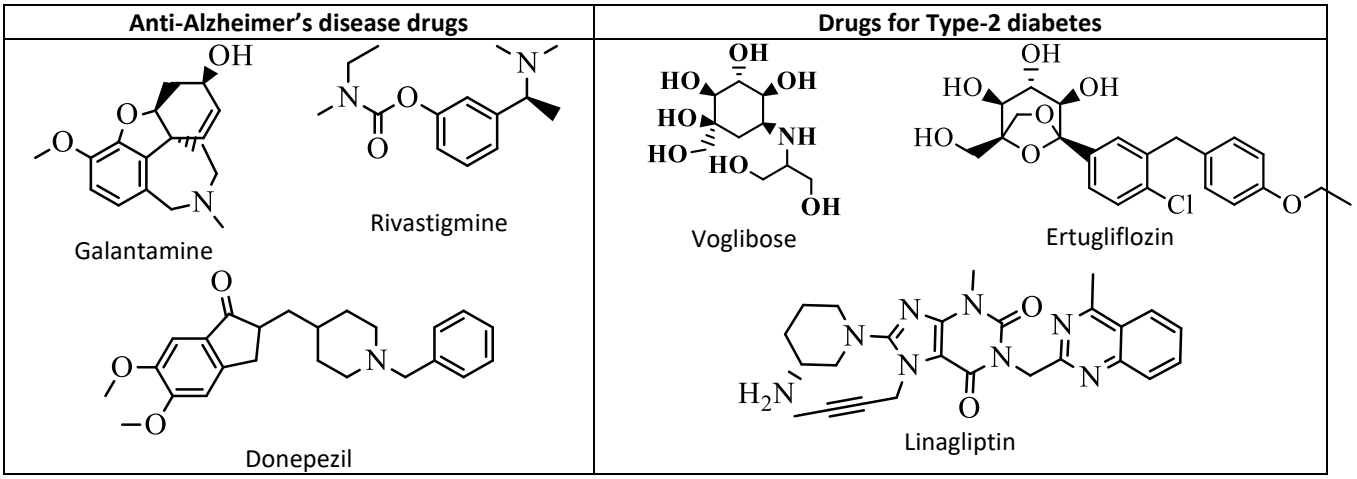


Figure 1. Some FDA-approved drugs to treat Alzheimer's disease and diabetes type II

effects [15]. Various biological action of ar-turmerone has led to the development of research on ar-turmerone.
In continuation, we investigated Ar-Turmerone (Ar-Tume) for Acetylcholine Esterase (AChE) inhibition and antidiabetic target as a natural product-based emerging scaffold.

Experimental

Materials and methods

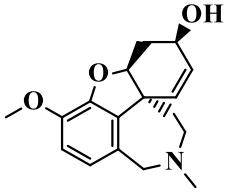
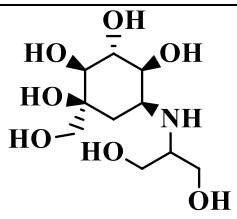
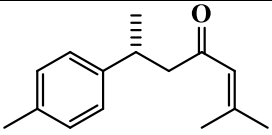
Preparation of receptor human Alzheimer's disease inhibitors and ligands

The crystal structure of human anticholinesterase (AChE) inhibitor (4PQE) under a resolution of 2.90 Å and the crystal structure of human salivary alpha-Amylase dimer (1XV8) hydrolase inhibitor under a resolution of 3.00 Å in PDB format was downloaded from Protein Data Bank (https://www.rcsb.org/). Galantamine (Gala, ChemSpider ID: 9272) and Voglibose (Vogl, ChemSpider ID: 392046) were taken from ChemSpider online platform (http://www.chemspider.com/) as a standard reference drugs. Ligands **1-3** (**Table 1**) were prepared using ChemDraw Ultra (Cambridge Soft Corporation USA) and obtained SMILES and .mol2 files were validated via Avogadro Software v1.2.0.

Biological characteristics evaluation and ADMET profile assay

Molinspiration biological characteristics of the selected compounds **1-3** were evaluated using Molinspiration Cheminformatics Online Server (https://www.molinspiration.com/) [16]. To evaluate ADMET properties, Swiss ADME algorithm (http://www.swissadme.ch) and pkCSM online servers (http://biosig.unimelb.edu.au/pkcsm/) were used.

Table 1. Selected reference drugs and Ar-Tumeroneas ligand

Chemical structures	Name of Compounds/Smiles	Molecular formula	Molecular weight	Docking score (kcal/mol)
 **Ligand 1**	Galantamine (Gala)	$C_{17}H_{21}NO_3$	287.35	-7.0 (against 4PQE)
 **Ligand 2**	Voglibose (Vogl)	$C_{10}H_{21}NO_7$	267.28	-6.1 (against 1XV8)
 **Ligand 3**	Ar-Tumerone (Ar-Tume)	$C_{15}H_{20}O$	216.32	-7.9 (against 4PQE) -6.7(against 1XV8)

Molecular docking studies against human anticholinesterase and antidiabetic hydrolase inhibitors

The Vinadock automation-assisted prediction of binding energies and interactive 3D visualization of results towards human anticholinesterase (AChE) inhibitor (4PQE: water molecules were deleted from the uploaded protein structure before docking) was used CB-Dock Online platform; server2 (http://cadd.labshare.cn/cb-dock2/) [10,17] concerning reference drugs.

Results and Discussion

Biological characteristics evaluation and prediction of ADMET properties

The biological activities of Gala, Vogl, and Ar-Tume were evaluated and presented in **Table 2**. Concerning the standard drug, Ar-Tume has shown the pronounced biological action profiles. For a novel drug discovery using pharmacokinetic and pharmacodynamics profiles, the validation of the drug is essentially recommended by researchers [17]. Therefore, it fundamentally required the safety criterion with significant efficacy [10,18].

The ADMET profiles for Gala, Vogl, and Ar-Tumehave been found to have significant positive characteristics concerning physicochemical properties, lipophilicity, drug-likeness, and medicinal chemistry parameters (**Table 3**) for targeted drugs calculated with Swissdock ADME and pkCSM platforms capped with biological-logarithms. Ar-Tume exhibited remarked performance and characteristics to a significant extent, similar to standard drugs. **Table 4** lists that Ar-Tume shows acceptable absorption parameters compared with the reference drug concerning Caco-2 permeability, Caco-2 permeability, human intestinal absorption, and skin permeability. Furthermore, **Table 5** provides considerable human volume of distribution and human fraction unbound (Fu) values, BBB, and CNS permeability for Ar-Tume. **Table 6** also explains that Ar-Tumeexhibitedgood effectiveness towards CYP2D6 substrate, CYP3A4 substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, and CYP3A4 inhibitor. **Table 7** demonstrates non-hepatotoxic, and no toxicity profiling was observed for Ar-Tume.

Molecular docking studies

Molecular docking is used to predict the orientation, type of interaction, and binding energy of selected molecular ligands in the interior of the binding site. **Figure 2** depicts the docking score for the active linkage of **Gala**, Vogl**,** and Ar-Tume against human anticholinesterase (AChE) inhibitor (4PQE) and human salivary alpha-Amylase dimer (1XV8) hydrolase inhibitor (**Table 1**) and as a result, the binding energies directs a significant ratio concerning the reference drug (**Table 1**,

Table 2. Molinspiration-predicted biological characteristics of selected drugs

Ligands	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Gala	0.93	0.26	-0.15	0.20	0.01	1.02
Vogl	0.14	0.16	0.10	0.09	0.34	0.85
Ar-Tume	-0.68	-0.46	-1.36	-0.14	-0.80	-0.25

Table 3. Physicochemical properties, lipophilicity, drug-likeness, and medicinal chemistry parameters for selected drugs calculated with Swissdock ADME and pkCSM

Drug targets	Swissdock ADME														pkCSM	
	Physicochemical Properties						Lipophilicity				Druglikeness		Med. Chem.			
	Fraction Csp3	NRB	HBA	HBD	MRef	TPSA (Å²)	iLOGP	XLOGP3	WLOGP	MLOGP	Lipinski violations	BioA Score	PAINS	SyAc	LogP	Surface Area
Gala	0.53	1	4	1	84.05	41.93	2.66	1.84	1.32	1.74	Yes; 0 violation	0.55	0	4.57	1.85	124.52
Vogl	1.0	5	8	8	59.04	153.6	0.88	-4.09	-4.49	-3.44	Yes; 1 violation: NHorOH>5	0.55	0	3.66	-4.49	104.12
Ar-Tume	0.40	4	1.0	0	69.75	17.07	2.91	3.98	4.02	3.68	Yes; 0 violation	0.55	0	2.40	4.02	98.18

NRB=No. Rotatable bonds; HBA=H-bonded acceptors; HBD=H-bonded donars;M^{Ref} =Molar refractivity; BioA=Bioavailability; and Sy^{Ac}=Synthetic accessibility.

Table 4. Absorption parameters for selected drugs calculated with pkCSM

Drug target	Distribution parameters				Excretion parameters	
	The human volume of distribution (VDss) (log L/kg) VDss low, log VDss<-0.15 VDss high, logVDss>0.45	Human fraction unbound (Fu)	BBB permeability (log BB) readily cross the BBB, logBB>0.3 poorly distributed, logBB<-1	CNS permeability (log PS) to Penetrate the CNS, logPS>-2 unable to penetrate the CNS, logPS<-3	Total Clearance (log ml/min/kg)	Renal OCT2 substrate
Gala	1.065	0.578	0.51	3.022	0.949	No
Vogl	-0.61	0.88	-1.57	-5.053	0.903	No
Ar-Tume	0.627	0.12	0.557	-1.763	0.293	No

NRB=No. Rotatable bonds; HBA=H-bonded acceptors; HBD=H-bonded donars;M^{Ref} =Molar refractivity; BioA=Bioavailability; and Sy^{Ac}=Synthetic accessibility.

Table 5. Distribution and excretion parameters for selected drugs calculated with pkCSM

Drug target	Distribution parameters				Excretion parameters	
	The human volume of distribution (VDss) (log L/kg) VDss low, log VDss<-0.15 VDss high, logVDss>0.45	Human fraction unbound (Fu)	BBB permeability (log BB) readily cross the BBB, logBB>0.3 poorly distributed, logBB<-1	CNS permeability (log PS) to Penetrate the CNS, logPS>-2 unable to penetrate the CNS, logPS<-3	Total Clearance (log ml/min/kg)	Renal OCT2 substrate
Gala	1.065	0.578	0.51	3.022	0.949	No
Vogl	-0.61	0.88	-1.57	-5.053	0.903	No
Ar-Tume	0.627	0.12	0.557	-1.763	0.293	No

Table 6. Metabolism parameters for selected drugs calculated with pkCSM

Drug target	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Gala	No	Yes	No	No	No	Yes	No
Vogl	No	No	No	No	No	No	No
Ar-Tume	No	No	Yes	No	No	No	No

Table 7. Toxicity parameters for selected drugs calculated with pkCSM

Drug target	AMES Toxicity[a]	Maximum Human tolerated Dose[b](log mg/kg/day) Toxic effect >0.477 log mg/kg/day	hERG I inhibitor[c]	hERG II inhibitor[d]	Oral Rat Acute Toxicity[e] (LD_{50}) (mol/kg)	Oral Rat Chronic Toxicity[f](LOAEL) (log mg/kg bw/day)	Hepatotoxicity[g]	Skin Sensitization[h]	*T. Pyriformis* toxicity[i] (Log ug/L)	Minnow toxicity[j] (Log mM)
Gala	No	-0.286	No	No	2.884	1.137	Yes	No	0.365	1.918
Vogl	No	2.186	No	No	1.989	5.053	No	No	0.285	6.178
Ar-Tume	No	0.787	No	No	1.611	1.235	No	Yes	2.292	-0.116

[a] A compound with positive values of AMES mutagenicity test is mutagenic and therefore may act as a carcinogen; A hERG[b] I/[c] II inhibitors could cause the development of the acquired long QT syndrome, which leads to the fatal ventricular arrhythmia; [d] A compound with positive tests could be associated with the disrupted normal function of the liver; [e] A compound with positive tests could have a high potential adverse effect for products applied to the skin, e.g., cosmetics and antifungals; m measured in log mg/kg/day. If the value is ≤ 0.477 log mg/kg/day is considered to be low, while > 0.477 log mg/kg/day is considered to be high; [g] is measured in mol/kg. [h] measured in log mg/kg_bw/day; [i] measured in log µg/L. If the value is< -0.5 log µg/L is considered to be toxic; [j] measured in log mM. If log LC_{50} values < -0.3 indicate high acute toxicity.

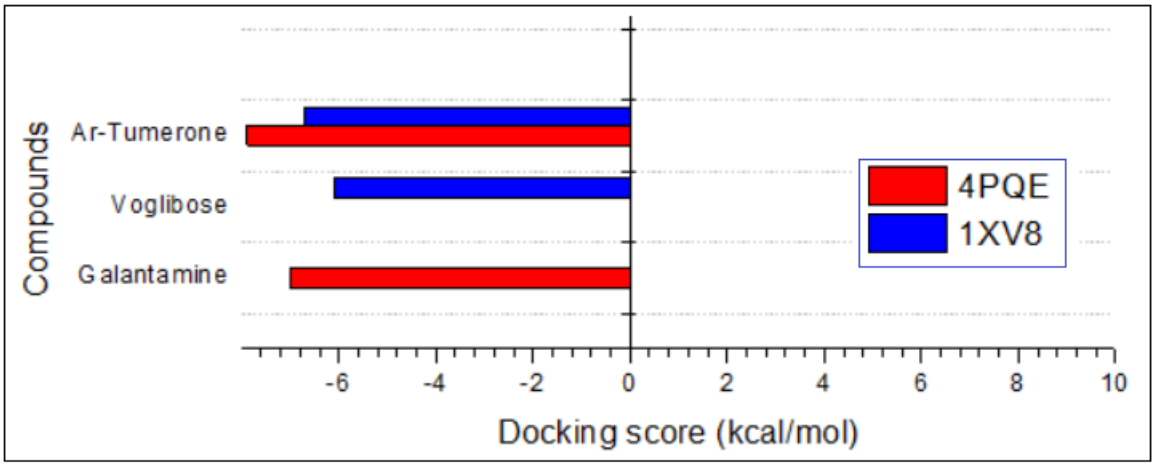


Figure 2. A comparative molecular docking score of Gala, Vogl, and Ar-Tume compounds

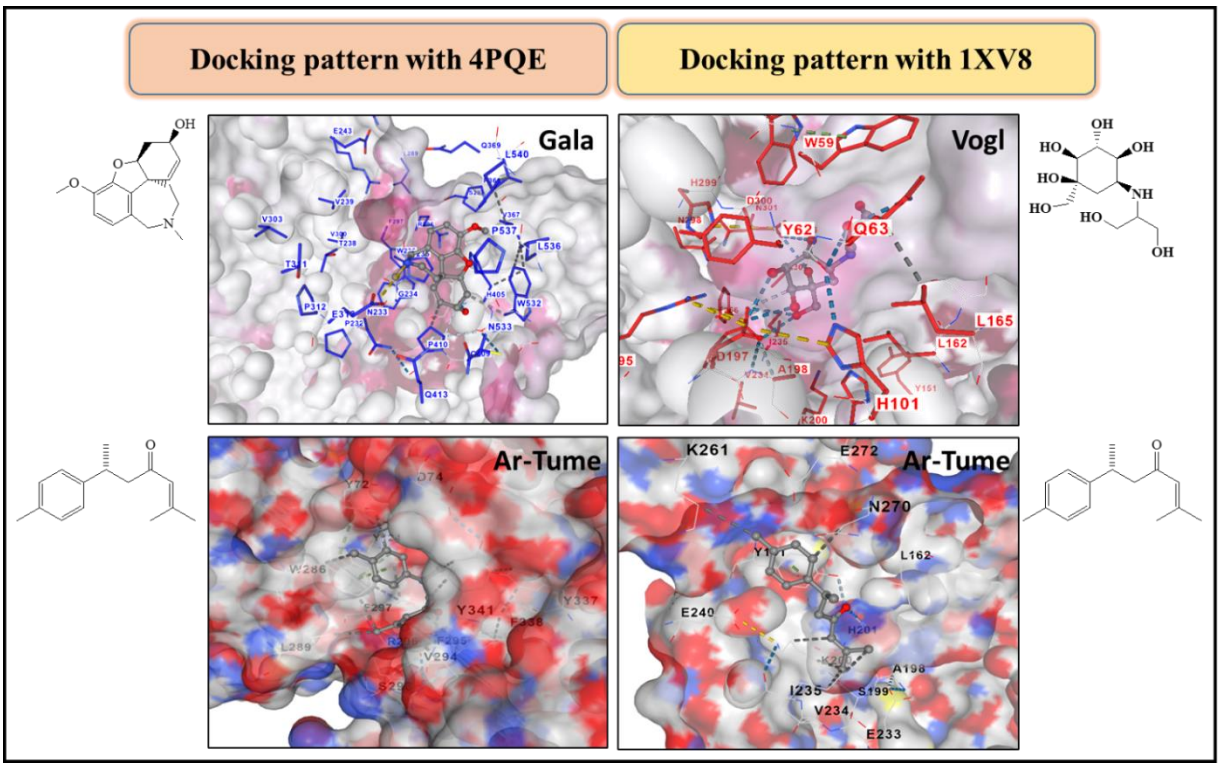


Figure 3. Molecular docking pattern of Gala, Vogland Ar-Tume ligands

Figures 2 and **3**). Plant-derived natural products are potentially important because of their inherent biological activities like antioxidant, antimicrobial, antidiabetic, etc. with environmental compatibility [15-17, 19, 20]. This study demonstrates that the selected compound Ar-Tume remarked to have mobile superior docking scores/negative binding energies concerning the reference drugs attributed to the strong hydrogen-bonding interactions in both inter and intra assemblies towards both anti-Alzheimers and antidiabetic capabilities.

Conclusion

Turmeric contains various natural phytoconstituents and has been found effective to have biological and therapeutic potential such as antimicrobial, anticancer, antidiabetic, and other health-related ailments. In the present study, Ar-Turmerone, one of the chief phytoconstituents present in *Curcuma longa* for human anticholinesterase (AChE) inhibitor (4PQE) and human salivary alpha-Amylase dimer (1XV8) hydrolase inhibitor as an emerging scaffold. This study reveals that the selected compound Ar-Tume showed remarked biological, ADMET profiling, and superior docking scores/ negative binding energies (-7.9 against 4PQE and -6.7 against 1XV8) concerning the reference drugs attributed to the strong hydrogen-bonding interactions both inter and intra assemblies towards both anti-Alzheimer's and antidiabetic capabilities which might further be used as oral therapeutics after clinical trials and these derivatives would be the initial step towards the exploration for biomedical applications with promising drug candidature to support in the treatment of neurologic disorders and diabetes in future.

Acknowledgments

Prof. S. A. Ahmed, Vice-Chancellor of Glocal University, is acknowledged for his moral support and critical suggestions.

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