Journal of Advances in Medical and Pharmaceutical Sciences

19(1): 1-14, 2018; Article no.JAMPS.45211
ISSN: 2394-1111

Impacts of Analogy and Dimerization of Bioactive Compounds on Molecular Biological Functions

Toluwase H. Fatoki[1*], Oladoja A. Awofisayo[2], Olusola A. Ogunyewo[1,3], Harriet U. Ugboko[4] and David M. Sanni[1]

[1]Enzyme Biotechnology and Bioinformatics Unit, Department of Biochemistry, Federal University of Technology, P.M.B. 704, Akure, Nigeria.
[2]Department of Pharmaceutical and Medicinal Chemistry, University of Uyo, P.M.B. 1017, Uyo, Nigeria.
[3]Microbial Engineering Group, International Centre for Genetic Engineering and Biotechnology, New Delhi, India.
[4]Department of Biological Sciences, Covenant University, P.M.B. 1023, Ota, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author THF designed the study, performed the computational analysis and wrote the first draft of the manuscript. Authors OAA and OAO managed the analyses of the study. Authors HUU and DMS provided relevant literature information. All authors edited the draft manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMPS/2018/45211
Editor(s):
(1) Dr. Palmiro Poltronieri, National Research Council of Italy, CNR-ISPA, Italy and Institute of Sciences of Food Productions, Operative Unit in Lecce, Italy.
Reviewers:
(1) Muhammad Highab Salisu, Federal University Dutse, Nigeria.
(2) Jacilene Silva, State University of Ceará, Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history/27905

Original Research Article

Received 02 September 2018
Accepted 08 November 2018
Published 21 December 2018

ABSTRACT

Aim: To determine the effect of analogy and dimerization of bioactive compounds at the molecular level on the biological functions.
Methodology: This work was carried out on a model set of bioactive compounds which consisted of resveratrol, piceatannol, isorhapontigenin, scirpusin A and scirpusin B, using computational methods which include target prediction, pharmacokinetics prediction, and molecular docking.
Results: It was observed that the increase in structural complexity reduces the solubility and gastrointestinal absorption but it does not affect the bioavailability score. The probability of target

**Corresponding author: E-mail: hezekiahfatoki@gmail.com;*

decreases with increasing structural complexity. In most of the targets, different molecular parameters were observed which exists between compound resveratrol and piceatannol as well as between scirpusin A and scirpusin B, while resveratrol, isorhapontigenin, and scirpusin B showed the related mode of molecular modulation in most of the targets.

Conclusion: The model of this study showed that natural bioactive dimer compounds have high binding affinity than its monomer in most cases and that usually with a different mechanism of action.

Keywords: Analogy; dimerization; resveratrol; piceatannol; scirpusin.

1. INTRODUCTION

Clustering of compounds by structural or property similarity can be a powerful approach to correlating compound features with biological activity and it has been widely utilised to identify structural redundancies and other biases in compound libraries [1]. Dimerization is an addition reaction in which two molecules of the same compound or analogue, react with each other to give adduct which has more efficacy or new functional properties. Dimerization may be homodimerization or heterodimerization, which is strongly dependent on the nature of the subunits and the attachment site of the subunits. Dimerization could result from condensation and reduction of functional groups. Although dimerization of biomolecules such as proteins (enzymes and receptors), carbohydrates and polyenes, have received much attention. There is no model study on the impact of analogy and Dimerization of bioactive compounds of microbial and plant sources. Dimerization occurs in nature by enzymatic and non-enzymatic oxidation [2]. The analogy and dimerization process could have great effect on the activity and stability of bioactive compounds, and it should lead scientists to the study and synthesis of dimeric compounds with therapeutic potentials on dimeric targets or multi-target of numerous diseases.

The existence of most of the targets in quaternary structure provides the basis for the functional potential of dimeric bioactive compounds. Wright and Usher [3], have extensively reviewed the approaches for designing multivalent binding bioactive compound dimers. Clustering analysis and similarity searching combined with target prediction is a recent approach for rational drug design of analogues of bioactive compounds [1]. It has been reported that many of the approved drugs have bioactive analogues with different targets [4], and they could be developed for clinical use through repurposing strategy. Therefore, there is an urgent need for studies on molecular evaluation of how analogous and Dimerization can affect the activities of therapeutant in the biological space, toward productive *in silico* drug design project. In this study, effects of analogous and Dimerization were evaluated computationally using a set of compounds which consisted of resveratrol (1), piceatannol (2), isorhapontigenin (3), scirpusin A (4) and scirpusin B (5), as a model as shown in Fig. 1.

Piceatannol (3,5,4',3'-trans-trihydroxystilbene), a natural polyphenolic stilbene phytochemical which was first isolated from the seeds of *Euphorbia lagascae* (Euphorbiaceae), is a naturally occurring hydroxylated analogue of resveratrol and has been also identified as a resveratrol metabolite [5,6]. Resveratrol (3,5,4'-trans-trihydroxystilbene) is found in plants such as peanuts, mulberries, blueberries, raspberries and grapes [7] and it has attracted increasing attention due to its multiple beneficial properties, including anti-cancer, anti-inflammatory and antioxidant activities [5,8]. Also, piceatannol shows activity similar to resveratrol [6] and its levels in plants such as grapes and wines are significantly lower than those of resveratrol [9] but much higher activity than resveratrol has been reported in few studies [10,11].

Scirpusin A, a hydroxystilbene dimer with anti-obesity and anti-adipogenic activity and inhibitory effects on amyloid-β aggregation [12]. Studies have shown that passion fruit (*Passiflora edulis*) seeds have a high piceatannol and scirpusin B content [10,13]. Piceatannol has various properties, such as sirtuin 1 (SIRT1) induction activity, a vasorelaxant effect, upregulation of endothelial nitric oxide synthase (eNOS) expression, promotion of collagen synthesis, inhibition of melanogenesis, and protection of the skin from ultraviolet B (UVB) irradiation [13,14], while Scirpusin B functional properties include vasorelaxing and anti-HIV effects [15].

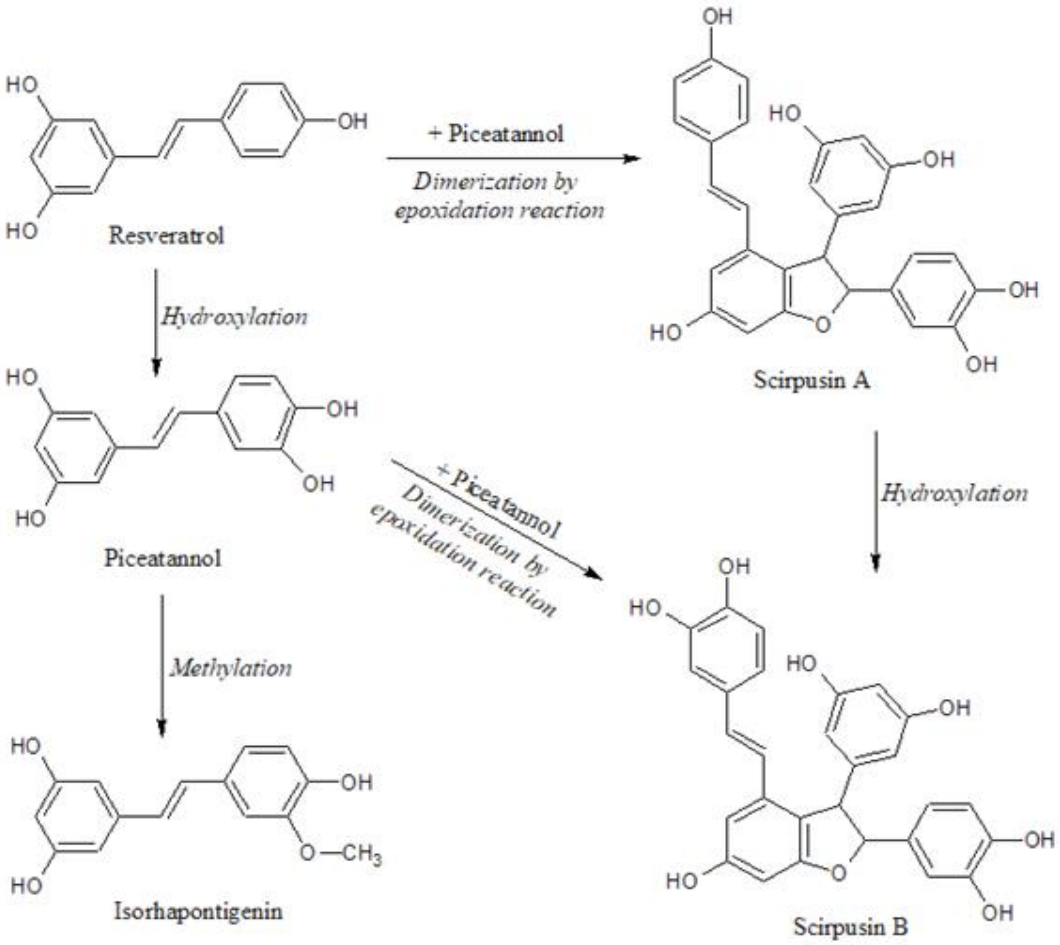

Fig. 1. Schematic of the model bioactive compounds

The previous study has shown that dimerization of the structure of the antimicrobial peptide Ctx-Ha lead to decrease in biological activity [16], while malyngolide dimer from marine Cyanobacterium *Lyngbya majuscule*, showed moderate *in vitro* antimalarial activity against chloroquine-resistant *Plasmodium falciparum* (W2) but roughly equivalent toxicity against H-460 human lung cell lines [17] as an antitumor agent. Antiviral activity of sets of novel bioactive hydroanthraquinones and anthraquinone dimers from a soft coral-derived *Alternaria sp*. The fungus has been reported [18]. These findings from pre-clinical studies have created high expectations for the therapeutic value of these bioactive compounds for the treatment of chronic diseases. The translational steps of clinical reports from cell and animal studies towards humans have turned out to be less than straightforward [19]. Therefore, dimerization is a new parameter that needs to be studied. These computational studies aimed to investigate the crucial impact of analogy and dimerization of bioactive compounds on biological functions in relevance to the discovery and development of novel therapeutants for unresolved diseases in our natural world.

2. MATERIALS AND METHODS

2.1 *In silico* Preparation of Ligands

The chemical structure of resveratrol, piceatannol, isorhapontigenin, scirpusin A and scirpusin B, were obtained from the PubChem Compound Database in sdf and canonical SMILES (Simplified Molecular Input Line Entry Specification) format. Ligand structures were constructed from SMILES for schematic (Fig. 1) using Chem Sketch software (http://www.acdlabs.com).

Table 1. Binding site residues and grid box parameters selected for the target proteins

Protein targets	Coverage	Center grid box (points)	Size (points)	Spacing (Å)	Predicted binding site residues
Aldo-keto reductase family 1 member B10 (PDB: 4JIH)	All	-24.356 x -29.766 x -1.971	120 x 110 x 120	0.375	Gly19, Thr20, Trp21, Lys22, Asp44, Tyr49, Lys78, His111, Ser160, Asn161, Gln184, Tyr210, Ser211, Pro212, Leu213, Gly214, Ser215, Pro216, Asp217, Leu229, Ala246, Ile261, Pro262, Lys263, Ser264, Val265, Thr266, Arg269, Glu272, Asn273
Aldose reductase (PDB: 1IEI)	All	2.934 x 0.779 x 2.339	110 x 110 x 116	0.375	Gly18, Thr19, Trp20, Lys21, Asp43, Tyr48, Lys77, His110, Trp111, Ser159, Asn160, Gln183, Tyr209, Ser210, Pro211, Leu212, Gly213, Ser214, Pro215, Asp216, Leu228, Ala245, Ile260, Pro261, Lys262, Ser263, Val264, Thr265, Arg268, Glu271, Asn272, Cys298
Prostaglandin G/H synthase 2 (Cyclooxygenase 2) (PDB: 5F1A)	A B	41.057 x 42.955 x 237.574 43.119 x 14.352 x 241.783	120 x 120 x 120 120 x 120 x 120	0.375 0.375	Tyr402, Gln406, Asn410, Ser412, Ile413, Glu416, His417
Carbonic anhydrase 12 (PDB: 4Q0L)	All	-0.326 x -18.839 x 0.002	120 x 120 x 110	0.375	His91, His93, Glu104, His117, Thr198
Estrogen receptor (PDB: 6B0F)	All	-32.312 x 16.761 x -22.633	110 x 120 x 120	0.375	Met343, Leu346, Thr347, Leu349, Ala350, Glu353, Trp383, Leu384, Leu387, Met388, Leu391, Arg394, Phe404, His524, Leu525
FAD-linked sulfhydryl oxidase ALR (PDB: 3U2L)	All	6.822 x 19.626 x 10.979	110 x 100 x 90	0.375	Arg99, Glu100, Gly103, Arg104, Ser106, Trp107, His111, Tyr140, Glu144, Cys145, Leu149, Cys171, His174, Asn175, Val177, Asn178, Lys180, Leu181, Lys183, Phe186, Arg194, Trp195
Tyrosine-protein kinase Lck (PDB: 3MPM)	All	15.130 x 12.764 x 46.336	110 x 110 x 120	0.375	Leu251, Val259, Ala271, Lys273, Glu288, Thr316, Glu317, Tyr318, Met319, Gly322, Ser323, Asp326, Ala368, Leu371, Asp382, Tyr394, Thr395, Arg397
Lysine-tRNA ligase (PDB: 6CHD)	A B	65.590 x 24.262 x -6.634 73.705 x -21.733 x -5.742	122 x 120 x 120 120 x 120 x 120	0.375 0.375	Arg323, Glu325, Thr330, His331, Asn332, Phe335, Thr337, Glu494, Ile495, Asn497, Gly550, Arg553, Ile564
Tyrosyl-DNA phosphodiesterase 1 (PDB: 1QZQ)	All	11.056 x 96.666 x 151.862	120 x 110 x 120	0.375	Phe202, Asn203, Tyr204, Cys205, Phe206, His228, Gly229, Ala253, Lys254, Leu255, Thr261, His262, His263, Thr264, Lys265, Ser265, Ser282, Asn283, Leu284, Tyr330, Thr358, Pro359, Ser536, Tyr537

2.2 Pharmacokinetic Prediction

The *in silico* ADME (Absorption, Distribution, Metabolism and Excretion) of the ligands were carried out using *SwissADME* server (http://www.swissadme.ch) and ADME screening was performed at default parameters [20].

2.3 Target Prediction

The identification of potential targets for the prepared ligands was carried out using the *Swiss Target Prediction* server (http://www.swisstargetprediction.ch). *Homo sapiens* were selected as the target organism [21]. The most probable targets were selected for molecular docking studies.

2.4 Molecular Docking Studies

The molecular docking studies were carried out according to the method of Sanni et al. [22]. The available crystal structure of the selected targets of the ligands (Table 1) were retrieved from the RCSB Protein Data Bank (PDB) (www.rcsb.org/pdb). All water molecules and heteroatoms were removed from the crystal structures using PyMOL molecular graphic system, version 2.0.7 (www.pymol.org). The *3D Ligand* Site [23], was used to predict the active site amino acid residues of the novel targets. All file conversions required for the docking study were performed using the open source chemical toolbox Open Babel version 2.4.1 [24]. The Gasteiger charge calculation method was used and partial charges were added to the ligand atoms prior to docking [25]. The pose and binding energy of each ligand on the targets were evaluated by blind docking parameters (Table 1) using AutoDock Tools (ADT) version 1.5.6 [26] and molecular docking program AutoDock Vina version 1.1.2 [27], was employed to perform the docking experiment from the command line. After docking, the ligands were ranked according to their binding energy and close interactions of binding of the target wit h the ligands were analysed and visualised using Auto Dock Tools.

3. RESULTS

The predicted ADME parameter for the model compounds used in this study (Table 2), showed that resveratrol and isorhapontigenin can cross the blood-brain barrier. It was observed that the increase in structural complexity of the compound reduces the solubility and gastrointestinal absorption but it does not affect the bioavailability score. The predicted active site cavity of these targets (Table 1) revealed the structure-activity relationship. It was observed from the model that the probability on target decreases with increasing structural complexity as shown in Table 3.

Table 2. Predicted pharmacokinetics parameters of the model compounds

Parameters	Bioactive compounds				
	1	**2**	**3**	**4**	**5**
Molecular Weight	228.24	244.24	258.27	470.47	486.47
Molar Refractivity	67.88	69.90	74.37	132.27	134.29
Total Polar Surface Area	60.69	80.92	69.92	130.61	150.84
Consensus LogP	2.38	2.14	2.63	3.69	3.26
ESOL Class	Soluble	Soluble	Soluble	Poorly Soluble	Poorly Soluble
Gastrointestinal Absorption	High	High	High	Low	Low
Blood Brain Barrier Permeant	Yes	No	Yes	No	No
P-glycoprotein Substrate	No	No	No	No	No
Lipinski Violations	0	0	0	1	1
Bioavailability Score	0.55	0.55	0.55	0.55	0.55
Synthetic Accessibility	2.02	2.09	2.22	4.53	4.57

1: Resveratrol; 2: Piceatannol; 3: Isorhapontigenin; 4: Scirpusin A; 5: Scirpusin B. Predicted parameters obtained from SwissADME server.
Resveratrol: C1=CC(=CC=C1C=CC2=CC(=CC(=C2)O)O)O
Piceatannol: C1=CC(=C(C=C1C=CC2=CC(=CC(=C2)O)O)O)O
Isorhapontigenin: COC1=C(O)C=CC(C=CC2=CC(O)=CC(O)=C2)=C1
Scirpusin A: C1=CC(=CC=C1C=CC2=CC(=CC3=C2C(C(O3)C4=CC(=C(C=C4)O)O)C5=CC(=CC(=C5)O)O)O)O
Scirpusin B: C1=CC(=C(C=C1C=CC2=CC(=CC3=C2C(C(O3)C4=CC(=C(C=C4)O)O)C5=CC(=CC(=C5)O)O)O)O)O

Table 3. Targets of the analogue and dimeric model compounds

Predicted targets	Target uniprot ID	Model bioactive compounds				
		1	2	3	4	5
Aldo-keto reductase family 1 member B10, B15	O60218, C9JRZ8				**	*
Aldose reductase	P15121				**	*
Prostaglandin G/H synthase 1	P23219,	*****	***	***	**	**
Prostaglandin G/H synthase 2	P35354		***	***	**	**
Carbonic anhydrase 1, 2, 3, 12	P00915, P00918, P07451, O43570	*****		**		
Carbonic anhydrase 4, 6	P22748, P23280	*****				
Estrogen receptor	P03372	*****	***	***		
Cytochrome P450 1A2, 3A4, 2C9	P05177, P08684, P11712	*****				
Cytochrome P450 1A2, 1B1	P05177, Q16678		***			
Microtubule-associated protein tau	P10636	*****	****			
Ribosyldihydronicotinamide dehydrogenase [quinone]	P16083	*****				
Amine oxidase [flavin-containing] A	P21397	*****				
Sodium-dependent noradrenaline transporter	P23975	*****				
FAD-linked sulfhydryl oxidase ALR	P55789		****	***		
Carbonic anhydrase 5A, 5B, 7, 9, 13, 14	P35218, Q9Y2D0, P43166, Q16790, Q8N1Q1, Q9ULX7			**		
Tyrosine-protein kinase Lck, HCK, Lyn, Blk	P06239, P08631, P07948, P51451		****			
Lysine--tRNA ligase	Q15046		****			
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8		****			
Dual specificity tyrosine-phosphorylation-regulated kinase 1A	Q13627		****			

*1: Resveratrol; 2: Piceatannol; 3: Isorhapontigenin; 4: Scirpusin A; 5: Scirpusin B. *(50-60%), **(60-70%), ***(70-80%), ****(80-90%), *****(90-100) Probability on Target. Predicted parameters obtained from SwissTargetPrediction server. Probabilities have been computed based on a cross-validation. They may therefore not represent the actual probability of success for any new molecule*

Table 4. Predicted binding free energies (docking scores) and detailed interactions observed between the ligands and the targets

Protein targets	Coverage	Novel targets with predicted binding energy (kcal/mol) and near binding residues				
		1	**2**	**3**	**4**	**5**
Aldo-keto reductase family 1 member B10 (PDB: 4JIH)	All	**-9.1** Gly19, Trp21, Thr30, Asp44, Tyr48, His111, Trp112, Tyr210, Ser211	-7.1 Trp21, Val48, His111, Phe123, Asn161	-7.2 Trp80, His111, Trp112, Phe123, Leu302	-8.9 Trp21, Trp80, His111, Phe123, Lys125, Trp220, Val301, Leu302,	-7.6 Ser163, Phe165, Gln166, Lys169, Ser305, Asp313
Aldose reductase (PDB: 1IEI)	All	-8.2 Trp20, Tyr48, Lys77, His110, Tyr209, Trp219, Cys298, Leu300	-7.5 Trp20, Val47, Tyr48, His110 Trp111, Cys298	-6.9 Trp20, Val47 Tyr48, Phe122	**-8.8** Trp20, Val47, Tyr48, Trp79, Trp111, Phe122, Pro218, Trp219, Leu300	-8.6 Trp20, Val47, Tyr48, Trp111, Phe122, Trp219, Leu300
Prostaglandin G/H synthase 2 (Cyclooxygenase 2) (PDB: 5F1A)	A	-6.4 Gln203, Leu391, Phe395, Tyr404, Ile408, Val444	**-8.4** Cys36, His39, Cys47, Pro153, Gln461, Glu465	-7.5 His39, Cys47, Gly136, Pro153, Pro154, Pro156, Gln461,	-7.7 Phe187, Pro189, Pro392, Thr394, Gln396, Lys401, Gln429, Ile430,	-7.9 Asn87, His90, Tyr91, Tyr475, Glu479, Gly483, Ly511, Pro514, Glu520,
	B	-6.4 Phe200, Gln203, Val295, His388, Leu391, Tyr404, Ile408, Val444,	-8.2 Ala202, Gln203, His207, Phe210, Thr212, Asn382, Trp387, His388	-8.0 Ala199, His207, Thr212, Ala202, Gln203, His207, Asn382, His386, His388	-8.2 His207, Lys211, Thr212, His214, Lys215, Asn222, Met273, Ile274, Gln289, Glu290	**-8.3** His207, Phe210, Lys211, Thr212, His214, Asn222, Ile274, Glu290, Val291,
Carbonic anhydrase 12 (PDB: 4Q0L)	All	-6.1 Thr5, Tyr6, Phe7, Arg240, Ile243, Asn244	-7.1 Gln89, His91, His117, Val119, Ala129, Ser130, Ser133, Leu197, Thr199	-6.4 Asn13, Gln27, Arg247, Gln250, Lys251, Arg255	**-8.6** Trp4, Asn64, His66, Lys69, Gln89, His91, Val119, Val141, Thr196, Leu197, Thr199, Trp208	-8.0 Asn13, Gly23, Leu26, Gln27, Gln250, Lys251, Asp253, Arg255
Estrogen receptor (PDB: 6B0F)	All	-5.8 Pro325, Ile326, Trp393, Arg394, Phe445, Lys449,	-7.1 Glu323, Pro324, Ile326, Glu353, Met357, Leu387, Trp393, Arg394, Lys449	**-7.8** Thr347, Ala350, Trp383, Leu384, Leu387, Ley525, Tyr526, Asn532, Val533	-7.6 Ala340, Met343, Leu525, Tyr526, Asn532, Val533	-6.7 Ser309, Leu310, Glu314, Ala318, Lys362, Arg363, Pro365, Gly366,
FAD-linked sulfhydryl oxidase ALR	All	-5.9	-6.2	-6.0	-7.4	**-7.6**

Protein targets	Coverage	Novel targets with predicted binding energy (kcal/mol) and near binding residues				
		1	**2**	**3**	**4**	**5**
(PDB: 3U2L)		His134, Pro156, His157, Arg150, Leu153	Arg99, Glu100, Gly103, Arg104, Trp107, His174, Lys183, Trp195,	Ile133, His134, Arg150, Lys151, Leu153, His157, Pro158	Gln126, Ala130, His157, Pro158, Thr160	Gln126, Ala130, Leu153, His157, Pro158, Thr160
Tyrosine-protein kinase Lck (PDB: 3MPM)	All	-7.9 Ala271, Lys273, Met319, Leu371, Asp391, Tyr394	-6.2 Arg299, Asn339, Leu342, Asp343, Gln347, Glu350, Glu495	-7.9 Val259, Lys273, Met319, Asp382, Asp391, Tyr394, Thr395	-7.0 Glu458, Tyr489, Ser492, Val493, Phe497	**-8.3** Leu251, Ala271, Tyr318, Met319 Ser323, Leu371
Lysine-tRNA ligase (PDB: 6CHD)	A	-5.8 Thr330, Met491, Lys492, Lys493	-7.7 Gly277, Arg323, Phe335, Asn497, Gly548, Gly550, Arg553	-7.0 Gly277, Ala278, Arg323, His331, Phe335, Met469, Arg553	-8.0 Tyr95, Arg131, Ile181, Ser207, Cys209, Leu210, His211, Tyr231	**-8.8** Arg420, Pro437, Arg438, Thr439, Thr440, Ile468, Ala518
	B	-6.1 Lys98, Phe99, Ala129, Leu206	-6.9 Gly277, Arg323, Phe335, Asn497, Arg553	-7.6 Arg323, His331, Asn332, Phe335, Arg485, Arg553	-7.9 Tyr95, Arg131, Ile181, Ser207, Cys209, Leu210, His211, Tyr231	**-8.1** Thr330, His331, Lys446, Gly449, Glu450, Glu453, Glu594, Arg553
Tyrosyl-DNA phosphodiesterase 1 (PDB: 1QZQ)	All	-6.9 Ser385, Asn388, Glu390, Leu423, Glu426, Lys428,	-7.3 Arg586, Tyr594, Lys596 Ala597	-7.0 Ser385, Ala389, Glu390 Thr422, Glu426, Ser433,	-9.0 Val444, Glu446, Asp585, Arg586, Tyr594, Lys596, Ala597	**-9.4** Tyr204, His263, Ser399, Pro441, Ser463, Thr466, His493, Ser518, Ala521

1: Resveratrol; 2: Piceatannol; 3: Isorhapontigenin; 4: Scirpusin A; 5: Scirpusin B. Predicted parameters generated from AutoDock Vina and AutoDock Tools

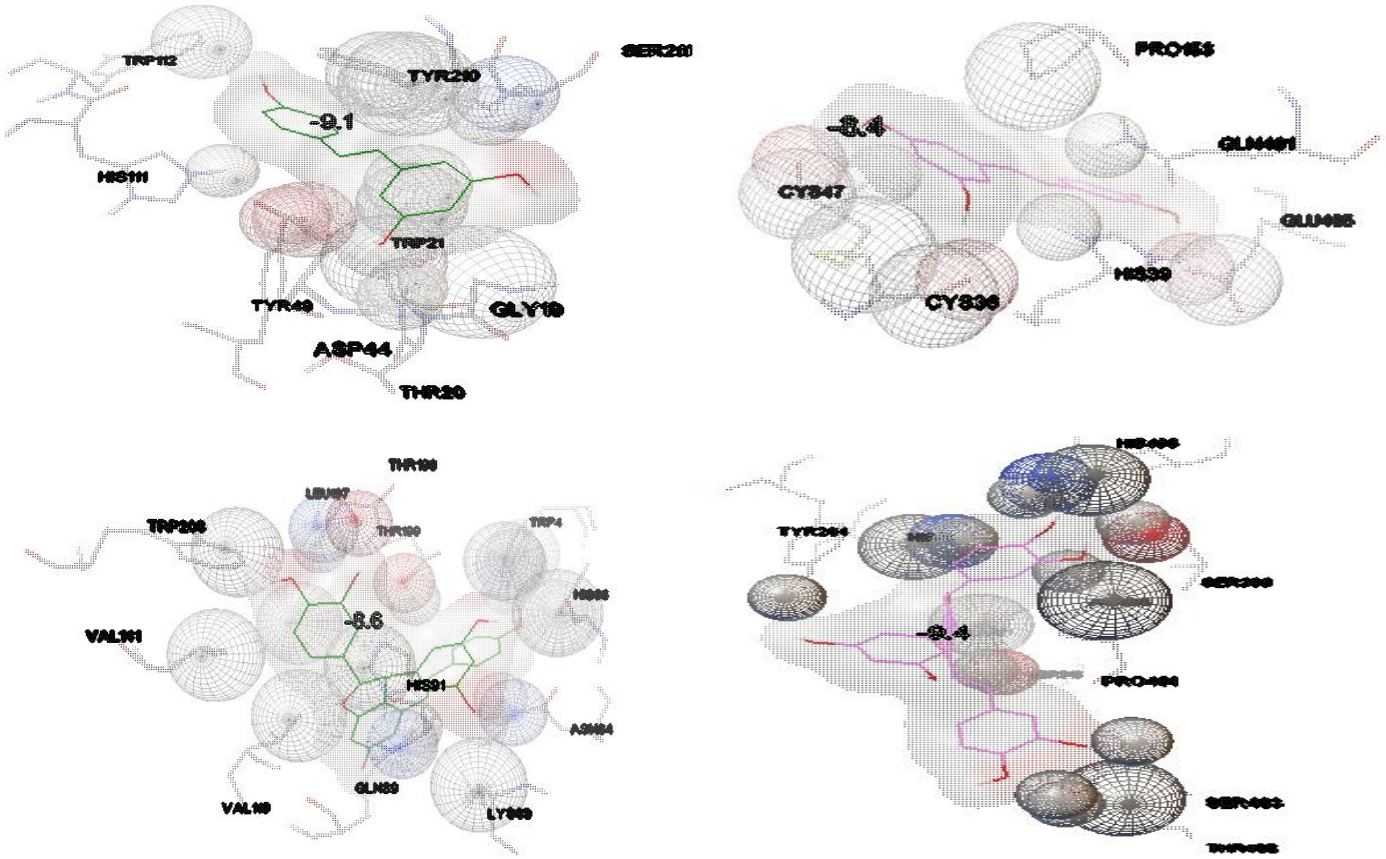

Fig. 2. Binding pose and score of resveratrol with 4JIH (-9.1 kcal/mol); Piceatannol with 5F1A (-8.4 kcal/mol); Scirpusin A with 4Q0L (-8.6 kcal/mol) and Scirpusin B with 1QZQ (-9.4 kcal/mol), generated from autodock tools

All the compounds in the model showed an affinity for prostaglandin G/H synthase 1 (cyclooxygenase 1, COX-1), with the highest probability of inhibition by resveratrol, while resveratrol was not found as a probable inhibitor of COX-2. Some of the targets in Table 3 were selected for docking analysis as shown in Table 4. The criterium used for selection of the target was the presence of two or more compounds of the model acting on the same target, and focus was on piceatannol rather than resveratrol. This help in the evaluation of the structural differences which might have been the critical factor. It was observed from the model that binding affinity to the targets varies, and this showed the critical impact of the analogue components and dimer components, on the biological function (Table 4).

Comparison of near binding residues from docking poses in Table 4 to the predicted binding residues of the active site of the targets in Table 1, showed that model compounds 1-4 bind to the active site of aldo-keto reductase family 1 member B10 (PDB: 4JIH) while compound 5 binds to its allosteric site; compounds 1-5 bind to the active site of aldose reductase (PDB: 1IEI); compounds 1-5 bind to the allosteric site of Prostaglandin G/H synthase 2 (PDB: 5F1A); compounds 2 and 4 binds to the active site of carbonic anhydrase 12 (PDB: 4Q0L) while compound 1, 3 and 5 binds to its allosteric site; compounds 2-4 binds to the active site of estrogen receptor (PDB: 6B0F) while compounds 1 and 5 binds to its allosteric site; compound 2 binds to the active site of FAD-linked sulfhydryl oxidase ALR (PDB: 3U2L) while compounds 1, 3-5 binds to its allosteric site; compounds 1, 3 and 5 binds to the active site of tyrosine-protein kinase Lck (PDB: 3MPM) while compounds 2 and 4 binds to its allosteric site; compounds 2 and 3 binds to the active site of lysine-tRNA ligase (PDB: 6CHD) while compounds 1, 4 and 5 binds to its allosteric site; and compound 5 bind to the active site of tyrosyl-DNA phosphodiesterase 1 (PDB: 1QZQ) while compounds 1-4 binds to its allosteric sites.

The interaction of the near binding residues of the compounds of the model on selected targets were shown in Fig. 2. Varied impact of the group that make up the analogue monomer or dimer was observed. In most of the targets, different molecular parameters were observed between compound 1 (resveratrol) and compound 2 (piceatannol) as well as between compound 4 (scirpusin A) and compound 5 (scirpusin B).

4. DISCUSSION

The partition coefficient (LogP) and solubility coefficient (LogS) interplay to define the bioavailability score (BS). The synthetic accessibility score (S) ranges between 1 (easy to make) and 10 (very difficult to make), while for a drug-like compound, 5 ≤ lipophilicity ≥ 0 ≤ hydrophilicity ≥ -5, and according to Lipinski's rule, one violation is acceptable [1,28]. The study has shown that not only piceatannol itself but also its metabolite, isorhapontigenin, contributed to the upregulation of SIRT1 expression [13]. It has been reported that scirpusin B and not piceatannol, could increase coronary flow via production of nitric oxide and vasodilating prostanoids [29] and that scirpusin A has inhibitory effects on amyloid-β aggregation Riviere et al. 2010, protective role against DNA damage by singlet oxygen [30] as well inhibits the growth of colorectal cancer Her2/CT26 cells *in vivo* in mice [31]. The result of this study showed that sirpusin A and sirpusin B targeted aldo-keto reductase family 1-member B10 and B15 as well as aldose reductase, with high probability by sirpusin A than sirpusin B.

The result of this study as shown in Table 3 revealed novel targets that have not been studied. Targets that have been reported elsewhere in the literature that matched those in Table 3 include prostaglandin G/H synthase 2 (cyclooxygenase 2, COX-2) and estrogen receptor [32] as well as tyrosine-protein kinase [33,34]. Non-steroidal anti-inflammatory drugs target the cyclooxygenase enzymes (COX-1 and COX-2) to block the formation of prostaglandins [35]. COX enzymes are homodimers consisting of tightly associated monomers that dissociate only upon denaturation and only one monomer of the COX homodimer is active at a given time, but the mechanism governing its inter-monomer communication is unknown [35]. Thus, aspirin would have close structural similarity to the model compounds of this study.

Estrogen receptor (ER) is an example of nuclear receptors, an allosteric signalling protein. ER form homodimers based on canonical model signalling pathway [36]. Small-molecule ligands control the receptor activity through selective modulation, functional selectivity or biased signalling through structural mechanisms, but the mechanism governing ER inter-domain communication is unknown [36]. Thus, tamoxifen would have close structural similarity to the model compounds of this study. Flavin adenine

dinucleotide (FAD)-dependent sulfhydryl oxidase, named augmenter of liver regeneration (ALR) in humans, is a protein present in the intermembrane space of mitochondria which forms head-to-tail homodimers [37]. It is also referred to as Erv1 (essential for respiratory growth and viability 1) or hepatopoietin. Whether it plays a physiological role in liver development is not known [38]. Thus, FAD would have close structural similarity to the model compounds of this study. The study has also shown that piceatannol inhibits arginase and eNOS [39], of which both enzymes can exist in dimeric form.

In the study of the ligand-specific effect on signalling targets, Nwachukwu et al. [36] reported clusters of small molecules based on direct and indirect modulations of the targets, which showed the typical impact of analogous and dimerization. Allosteric drugs (binding to allosteric effector sites are considered to be better than orthosteric drugs (binding to active centres) and the concept of allosteric drug action to the interactome level has been articulated [40,41]. In this study, the interaction of the near binding residues of the compounds of the model on selected targets showed the impact of hydroxyl group variation in these compounds. Compound 1, 3 and 5 showed the related mode of molecular modulation in most of the targets. This suggests that the position where methylation occurred in compound 3 (isorhapontigenin) lead to no significant impact on the mode of action. If methylation had occurred on any of the carbon of the aromatic ring, the impact could have been different. Studies on pterostilbene (trans-3,5-dimethoxy-4′-hydroxystilbene), another analogue of resveratrol, has reported pharmacological properties similar to those of resveratrol, but with several advantages and more potency compared to resveratrol, including more lipophilicity, which increases oral absorption, possibly higher cellular uptake and longer half-life than resveratrol [42,43].

Many studies relating to the molecular mechanisms of small-molecule or large-molecule interactions have shown that the use of two or more separate binding events can be used to control biological interactions [3]. Therefore, multivalent interactions are fundamental to the regulation of several critical biological systems. Investigation of analogues and dimeric forms of the existing approved drugs could provide novel insight in the drug lead discovery process and cause revolutionary innovation in the pharmaceutical industry.

5. CONCLUSION

This study has shown the critical impact of analogy and dimerization of bioactive compounds at the molecular level on the biological functions. The model of this study showed that natural bioactive dimer compounds have high binding affinity than its monomer in most cases. The dimers have targets probable for its monomer and that usually with a different mechanism of action. Also, the nature of the group that makes the analogue of monomer or dimer compounds is fundamental for the outcome biological function. The combination of *in silico* targets, pharmacokinetics and molecular docking predictions showed that synthetic dimeric bioactive compounds with multi targets could be the next game-changer in therapeutant research and development.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study did not involve the use of animal or human in the lab. It was a computational study that makes use of existing curated raw biological information to predict the set of model compounds, which possibly represented what could be encounter during the drug discovery process.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sanni DM, Fatoki TH, Kolawole AO, Akinmoladun AC. Xeronine structure and function: Comparative mastery of its mystery. In Silico Pharmacology. 2017; 5(8):1-7.
   DOI: 10.1007/s40203-017-0028-y
2. Sugumaran M, Hennigan B, Semensi V, Dali H. On the nature of nonenzymatic and enzymatic oxidation of the putative sclerotizing precursor, 1,2-dehydro-N-acetyldopamine. Arch. Insect Biochem. Physiol. 1988;8:89–100.
3. Wright D, Usher L. Multivalent binding in the design of bioactive compounds. Current Organic Chemistry. 2001;5:1107-1131.

4. Hu Y, Eugen Lounkine E, Bajorath J. Many approved drugs have bioactive analogs with different target annotations. AAPS Journal. 2014;14:9621-9628.
DOI: 10.1208/s12248-014-9621-8
5. Jeong SO, Son Y, Lee JH, Cheong YK, Park SH, Chung HT, Pae HO. Resveratrol analog piceatannol restores the palmitic acid-induced impairment of insulin signaling and production of endothelial nitric oxide via activation of anti-inflammatory and antioxidative heme oxygenase-1 in human endothelial cells. Mol. Med. Rep. 2015;12:937–944.
6. Kershaw J, Kim KH. The therapeutic potential of piceatannol, a natural stilbene, in metabolic diseases: A review. J. Med. Food. 2017;20:427–438.
7. Weiskirchen S, Weiskirchen R. Resveratrol: How much wine do you have to drink to stay healthy? Adv Nutr. 2016; 7:706-718.
8. Shrotriya S, Tyagi A, Deep G, Orlicky DJ, Wisell J, Wang XJ, Sclafani RA, Agarwal R, Agarwal C. Grape seed extract and resveratrol prevent 4-nitroquinoline 1-oxide induced oral tumorigenesis in mice by modulating AMPK activation and associated biological responses. Mol Carcinog. 2015;54:291-300
9. Rodríguez-Cabo T, Rodríguez I, López P, Ramil M, Cela R. Investigation of liquid chromatography quadrupole time-of-flight mass spectrometry performance for identification and determination of hydroxylated stilbene antioxidants in wine. J. Chromatogr. A. 2014;1337:162–170.
10. Matsui Y, Sugiyama K, Kamei M, Takahashi T, Suzuki T, Katagata Y, Ito T. Extract of passion fruit (*Passiflora edulis*) seed containing high amounts of piceatannol inhibits melanogenesis and promotes collagen synthesis. J. Agric. Food Chem. 2010;58:11112–11118.
11. Kinoshita Y, Kawakami S, Yanae K, Sano S, Uchida H, Inagaki H, Ito T. Effect of long-term piceatannol treatment on eNOS levels in cultured endothelial cells. Biochem. Biophys. Res. Commun. 2013;430: 1164–1168.
12. Riviere C, Papastamoulis Y, Fortin PY, Delchier N, Andriamanarivo S, Waffo-Teguo P, Kapche GD, Amira Guebalia H, Delaunay JC, Merillon JM, Richard T, Monti JP. New stilbene dimers against amyloid fibril formation. Bioorg Med Chem Lett. 2010;20:3441-3443.
13. Kawakami S, Kinoshita Y, Maruki-Uchida H, Yanae K, Sai M, Ito T. Piceatannol and its metabolite, isorhapontigenin, induce SIRT1 expression in THP-1 human monocytic cell line. Nutrients. 2014;6: 4794–4804.
14. Kitada M, Ogura Y, Maruki-Uchida H, Sai M, Suzuki T, Kanasaki K, Yuna Hara Y, Seto H, Kuroshima Y, Monno I, Koya D. The effect of piceatannol from passion fruit (*Passiflora edulis*) seeds on metabolic health in humans. Nutrients. 2017;9:11-42.
DOI: 10.3390/nu9101142
15. Sano S, Sugiyama K, Ito T, Katano Y, Ishihata A. Identification of the strong vasorelaxing substance scirpusin B, a dimer of piceatannol, from passion fruit (*Passiflora edulis*) seeds. J. Agric. Food Chem. 2011;59:6209–6213.
16. Lorenzón EN, Cespedes GF, Vicente EF, Nogueira LG, Bauab TM, Castro MS, Cilli EM. Effects of dimerization on the structure and biological activity of antimicrobial peptide Ctx-Ha. Antimicrobial Agents and Chemotherapy. 2012;56(6):3004–3010.
17. Gutiérrez M, Tidgewell K, Capson TL, Engene N, Almanza A, Schemies J, Jung M, Gerwick WH. malyngolide dimer, a bioactive symmetric cyclodepside from the panamanian marine cyanobacterium lyngbya majuscule. J Nat Prod. 2010; 73(4):709–711.
DOI: 10.1021/np9005184
18. Zheng C, Shao C, Guo Z, Chen J, Deng D, Yang K, Chen Y, Fu X, She Z, Lin Y, Wang C. Bioactive hydroanthraquinones and anthraquinone dimers from a soft coral-derived *Alternaria* sp. fungus. Journal of Natural Product. 2012;75:189−197.
DOI: 10.1021/np200766d
19. Szkudelski T, Szkudelska K. Resveratrol and diabetes: From animal to human studies. Biochim. Biophys. Acta. 2015; 1852:1145–1154.
20. Daina A, Michielin O, Zoete V. Swiss ADME: A free web tool to evaluate pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017;7: 42717.
DOI: 10.1038/srep42717
21. Gfeller D, Michielin O, Zoete V. Shaping the interaction landscape of bioactive molecules. Bioinformatics. 2013;29:3073-3079.
22. Sanni DM, Lawal OT, Fatoki TH, Salawu SO. Insilico phylogenetics and molecular

docking studies of rhodanese from yeast. Journal of Advances in Biology and Biotechnology. 2018;17(4):1-10.

23. Wass MN, Kelley LA, Sternberg MJ. 3D ligand site: Predicting ligand-binding sites using similar structures. Nucleic Acids Research. 2010;38:W469-73.
24. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open babel: An open chemical toolbox. Journal of Chem Informatics. 2011;3:33.
25. Gasteiger J, Marsili M. Iterative partial equalization of orbital electronegativity - a rapid access to atomic charges. Tetrahedron. 1980;36(22):3219–28.
26. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. autodock4 and autodock tools4: Automated docking with selective receptor flexibility. Journal of Computational Chemistry. 2009;30(16):2785–91.
27. Trott O, Olson AJ. AutoDock vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry. 2010; 31(2):455–61.
28. Lipinski CA, Lombardo F, Dominy V, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews. 2001;46:3–26.
29. Matsumoto Y, Gotoh N, Sano S, Sugiyama K, Ito T, Abe Y, Katano Y, Ishihata A. Effects of scirpusin B, a polyphenol in passion fruit seeds, on the coronary circulation of the isolated perfused rat heart. Int J Med Res Health Sci. 2014; 3(3):547-553.
30. Kong Q, Ren X, Jiang L, Pan Y, Sun C. Scirpusin A, a hydroxystilbene dimer from Xinjiang wine grape, acts as an effective singlet oxygen quencher and DNA damage protector. J Sci Food Agric. 2010;90:823-828.
31. Hong E, Heo E, Song J, Kwon B, Lee J, Park Y, Kim J, Chang S, Chin Y, Jeon S, Ko H. Trans-scirpusin A showed antitumor effects via autophagy activation and apoptosis induction of colorectal cancer cells. Oncotarget. 2017;8(25):41401-41411.
32. Kulkarni SS, Cantó C. The molecular targets of resveratrol. Biochimica et Biophysica Acta. 2015;1852;1114–1123.
33. Geahlen RI, Mclaughlin JI. Piceatannol (3,4,3′,5′-tetrahydroxytrans-stilbene) is a naturally occurring protein-tyrosine kinase inhibitor. Biochem. Biophys. Res. Commun. 1989;165:241–245.
34. Wung BS, Hsu MC, Wu CC, Hsieh CW. Piceatannol upregulates endothelial heme oxygenase‐1 expression via novel protein kinase C and tyrosine kinase pathways. Pharmacol Res. 2006;53:113-122.
35. Lucido MJ, Orlando BJ, Vecchio AJ, Malkowski MG. The crystal structure of aspirin acetylated human cyclooxygenase-2: Insight into the formation of products with reversed stereochemistry. Biochemistry. 2016;55(8):1226–1238.
DOI: 10.1021/acs.biochem.5b01378
36. Nwachukwu JC, Srinivasan S, Zheng Y, Wang S, Min J, Dong C, Lioa Z, Nowak J, Wright NJ, Houtman R, Carlson KE, Josan JS, Elemento O, Katzenellenbogen JA, Zhou H, Nettles KW. Predictive features of ligand-specific signaling through the estrogen receptor. Molecular Systems Biology. 2016;12:864-877.
DOI: 10.15252/msb.20156701
37. Banci L, Bertini I, Calderone V, Cefaro C, Ciofi-Baffoni S, Gallo A, Tokatlidis K. An electron-transfer path through an extended disulfide relay system: The case of the redox protein ALR. Journal of the American Chemical Society. 2012;134: 1442−1445.
Available:http//dx.doi.org/10.1021/ja20988 1f
38. Herrmann JM, Reimer J. Mitochondrial disulfide relay: Redox-regulated protein import into the intermembrane space. Journal of Biological Chemistry. 2012; 287(7):4426–4433.
DOI: 10.1074/jbc.R111.270678
39. Nguyen MC, Ryoo S. Intravenous administration of piceatannol, an arginase inhibitor, improves endothelial dysfunction in aged mice. Korean J Physiol Pharmacol. 2017;21(1):83-90.
DOI: 10.4196/kjpp.2017.21.1.83
40. Nussinov R, Tsai CJ, Csermely P. Allo-network drugs: Harnessing allostery in cellular networks. Trends Pharmacol. Sci. 2011;32:686-693.
41. Nussinov R, Tsai CJ. The different ways through which specificity works in orthosteric and allosteric drugs. Curr Pharm Des. 2012;18:1311-1316.

42. McCormack D, McFadden D. Pterostilbene and cancer: Current review. J. Surg. Res. 2011;173:e53−e61.
43. Chiou YS, Tsai ML, Nagabhushanam K, Wang YJ, Wu CH, Ho CT, Pan MH. Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. J. Agric. Food Chem. 2011;59: 2725−2733.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/27905