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Original Article

Docking Analysis of 17 Selected Artoindonesianins as Human Neutrophil Elastase, Matrix Metalloproteinase 9 and G9A like Protein Lysine Methyl Transferase Modulating agents.

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ABSTRACT

Background and Objectives: The several Artoindonesianins have been reported from different *Artocarpus* species, and they are known for various biological activities. In the current investigation, we aimed to study 17 chosen Artoindonesianins of *Artocarpus* species as potent modulating agents of human Neutrophil Elastase (hNE), human Matrix Metalloproteinase 9 (hMMP 9) and human G9A like Protein Lysine Methyl Transferase (hPKMT) using molecular docking method. **Materials and Methods:** The 17 chosen Artoindonesianins of *Artocarpus* species were studied on the docking behaviour of hNE, hMMP 9 and hPKMT by utilizing the Swiss dock approach. **Results**: The docking investigation showed that Artoindonesianin L (hMMP 9) and Artoindonesianin U (hNE and hPKMT) of *Artocarpus* species has exhibited the maximum binding energy (-9.14, -8.03 and -9.28 kcal/mol) with three target enzymes hMMP 9, hNE, and hPKMT respectively. **Conclusion**: Thus, the present finding gives new insight about the 17 selected Artoindonesianins of *Artocarpus* species as potent modulating agents of human Neutrophil Elastase (hNE), human Matrix Metalloproteinase 9 (hMMP 9) and human G9A like protein Lysine Methyl Transferase (hPKMT) which will aid in managing cancer, inflammation, photo-aging and wounds.

Keywords: *Artocarpus* species, Artoindonesianins, Docking, Good health and well-being, Human G9A like Protein Lysine Methyl Transferase, Human Matrix Metalloproteinase 9, Human Neutrophil Elastase.

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INTRODUCTION

The genus *Artocarpus* comprises of fifty species, which are distributed in tropical and subtropical regions of Asia (Rao *et al*., 2010). "*Artocarpus*" is derived from the Greek word 'artos' and 'karpos' which means 'bread' and 'fruit' respectively. Bread fruits are rich source of carbohydrates and minerals consuming it helps to overcome malnutrition (Buddhisuharto *et al*., 2021). Especially bread fruit seeds are rich in i) Manganese (Mn), ii) Magnesium (Mg), iii) Potassium (K), iv) Calcium (Ca), v) Iron (Fe) and lectins which meet up the nutritional requirements for the poor people (Khan *et al*., 2021). *Artocarpus* species are abundant in phenols, flavonoids, stilbenoids, arylbenzofurons and lectin (Baliga *et al*., 2011). Preclinical studies have reported that it possesses antifungal, anti-neoplastic, hypoglycemic and wound healing activities.

The *Artocarpus* genus are an important natural source of phytochemicals like i) artocarpin-A, ii) artocarpin-B, iii) morin, iv) dihydromorin, v) cynomacurin, vi) artocarpin, vii) cyloartocarpin, viii) artocarpesin, ix) oxydihydroartocarpesin, x) artocarpetin, xi) norartocarpetin, xii) cycloartinone, xiii) ursolic acid, xiv) β-sitosterol, xv) betulinic acid, xvi) artocarpanone, and xvii) heterophylol (Somashekhar *et al*., 2013). Apart from these several prenylated flavonoids have been reported from various *Artocarpus* species and each phytochemical is unique to specific *Artocarpus* species. For instance, i) both Artoindonesianin A and Artoindonesianin B have been isolated from the roots of *Artocarpus champeden* (Hakim *et al*., 1999); ii) Artoindonesianin P was obtained from *A. lanceifolius* (Hakim *et al*., 2002); while Artoindonesianin L has been reported from *A. rotunda* (Suhartati *et al*., 2001); similarly Artoindonesianin C has been isolated from *A. elasticus* (Fajriah *et al*., 2022). Further, two more (Artoindonesianin O and N) have been reported from *A. gomezianus* (Hakim *et al*., 2002). Four Artoindonesianins (namely Artoindonesianins Q. R, S and T) have been reported

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from *A. champeden* (Syah *et al*., 2002). Similarly, two more Artoindonesianins (Artoindonesianins U and V) have been reported from *A. champeden* (Syah *et al*., 2004). Artoindonesianin E1 (oxepinoflavone) has been reported from *A. elasticus* (Musthapa *et al*., 2009); another Artoindonesianin (Artoindonesianin J) has been reported from *A. bracteata* (Ersam *et al*., 2002). Further two more Artoindonesianins (Artoindonesianins X and Y) have been reported from *A. fretessii* (Soekamto *et al*., 2003).

The earlier studies engaged us to carry out the current investigation on 17 chosen Artoindonesianins (Artoindonesianin A, B, B1, C, E1, J, L. N, O, P, Q, R, S, T, U, V and Y) which were aimed to investigate on the docking analysis of human neutrophil elastase (hNE), human matrix metalloproteinase 9 (hMMP 9) and human G9A like protein lysine methyl transferase (hPKMT) by using the swissdock method, which aids in developing anti-inflammatory/ anti-cancer agents for managing inflammation and cancer related disorders.

MATERIALS AND METHODS

Ligand preparation

The chemical structures of 17 selected Artoindonesianins ligands were selected for the present investigation based on previous reports, that includes 1) Artoindonesianin A (CID 10603133), 2) Artoindonesianin B (CID 10096171), 3) Artoindonesianin B1 (CID 71307312), 4) Artoindonesianin C (CID 10552003), 5) Artoindonesianin E1 (CID 70678703), 6) Artoindonesianin J (CID 15549721), 7) Artoindonesianin L (CID 163184360), 8) Artoindonesianin N (CID 71626927), 9) Artoindonesianin O (CID 15700061), 10) Artoindonesianin P (CID 10316935), 11) Artoindonesianin Q (CID 5320428), 12) Artoindonesianin R (CID 5320437), 13) Artoindonesianin S (CID 5320444), 14) Artoindonesianin T (CID 5320451), 15) Artoindonesianin U (CID 10030972), 16) Artoindonesianin V (CID 10053761), 17) Artoindonesianin Y (CID 641711), 18) Sivelestat - hNE reference compound1 (CID 107706), 19) Artoindonesianin F - hNE reference compound2, 20) Caffeic acid – hMMP 9 reference compound1 (CID 689043), 21) Genistein – hMMP 9 reference compound2 (CID 5280961), 22) BIX-01294 – hPKMT reference compound1 (CID 124219522) and 23) MS8511 – hPKMT reference compound2 (CID 164512403) were downloaded from PubChem compound database. These 17 selected Artoindonesianins and 6 reference compounds structures were drawn and prepared by using ChemDraw 2D and 3D software tools (Mohan *et al*., 2022). Thus, these prepared three-dimensional structures were used for further studies (swissdock).

Preparation of target enzymes

The three-dimensional [3-D] structures of human neutrophil elastase [hNE] (PDB◘◘ ID: 1H1B with a resolution of 2.00 A°), human matrix metalloproteinase 9 [hMMP 9] (PDB◘◘ ID: 4H1Q with a resolution of 1.59 A°) and human G9a-like protein lysine methyltransferase (hPKMT) (PDB◘◘ ID: 3FPD with a resolution of 2.40 A°) was downloaded from ◘◘Protein Data Bank (PDB) databases respectively. 'A' chain of all three enzymes (hNE, hMMP 9 and hPKMT) were prepared independently by removing other chains, ligands, and even the crystallographically observed "water" (H_2O) molecules by using UCSF Chimera software tool (Mohan *et al*., 2022).

Toxicity analysis

Toxicity analysis was performed for 17 chosen Artoindonesianins through the 'pkCSM' free online server (Prakash *et al*., 2023).

Docking study

A docking studies was performed for 17 chosen Artoindonesianins with three target proteins (hNE, hMMP 9 and hPKMT) using the Swissdock free online server (Prakash *et al*., 2023). Finally, PLIP (Protein-Ligand Interaction Profiler) free web server was utilized to analysis the binding site of best-docked pose for each ligand (Srinivasan *et al*., 2023).

Statistical analysis

Docking protocol was validated using sivelestat (hNE), caffeic acid (hMMP 9) and BIX-01294 (hPKMT) as reference compounds. And the Root Mean Square Deviation [RMSD**] analysis of all the docked complexes (17 target ligands) was separately compared with that of (reference compounds) docked complex for each chosen target enzymes by utilizing the 'align' command in "PyMOL" software (Ramsbottom *et al*. 2018, Narayanaswamy *et al*. 2024).

In present investigation, no experimental animals (or) human subjects were used, thus ethical approval was not needed.

RESULTS

In the present study, Table 1 represents the toxicity analysis of 17 chosen Artoindonesianins (ligands), in which two ligands (Artoindonesianin C and P) were predicted to possess hepatotoxicity nature.

The current molecular docking analysis showed that Artoindonesianin U has the Highest Binding Energy (HBE) (-8.03 kcal/mol) with the Human Neutrophil Elastase (hNE). In contrast, Artoindonesianin A had the minimum binding energy (MBE) (-6.29 kcal/mol) with the human Neutrophil Elastase (hNE) (as shown in Table 2).

Eleven ligands (Artoindonesianin B1, C, E1, J, N, Q, R, S, T, V and Y) have shown interactions with Ser 195 amino acid residue of human Neutrophil Elastase (hNE). Similarly, eight ligands (Artoindonesianin B1, C, L, N, O, R, V and Y) have shown interaction with His 57 amino acid residue of human Neutrophil Elastase (hNE). However, one ligand (Artoindonesianin A) does not show any hydrogen bond interaction with the amino acid

residue of human neutrophil elastase (hNE), as shown in Figure 1a.

The present molecular docking results showed that Artoindonesianin L has the Maximum Binding Energy (MBE) (-9.14 kcal/mol) with the Human Matrix Metalloproteinase (hMMP 9) enzyme. On the other hand, Artoindonesianin A had the least binding energy (LBE) (-6.57 kcal/mol) with the human Matrix Metalloproteinase (hMMP 9) enzyme (as shown in Table 3).

Seven ligands (Artoindonesianin J, L, P, Q, S, U and Y) have shown interactions with Gln 227 amino acid residue of human Matrix Metalloproteinase (hMMP 9). Similarly, four ligands (Artoindonesianin C, P, S and V) have shown interaction with Tyr 248 amino acid residue of human Matrix Metalloproteinase (hMMP 9). However, three ligands (Artoindonesianin B [as shown in Figure 1b, E1 and J) do not show any hydrogen bond interaction with the amino acid residue of Human Matrix Metalloproteinase (hMMP 9).

The present molecular docking analysis showed that Artoindonesianin U has the Highest Binding Energy (HBE) (-9.28 kcal/mol) with the human G9a-like protein lysine methyltransferase (hPKMT). In contrast, Artoindonesianin V had the Minimum Binding Energy (MBE) (-6.61 kcal/mol) with the human G9a-like Protein Lysine Methyltransferase (hPKMT) (as shown in Table 4).

Four ligands (Artoindonesianin B1, N, T and U) have shown interactions with Trp 1107 amino acid residue of human G9a-like protein lysine Methyltransferase (hPKMT). Similarly, four ligands (Artoindonesianin B1, P, R and T) have shown interaction with Arg 1226 amino acid residue of human G9a-like protein lysine Methyltransferase (hPKMT). However, one ligand (Artoindonesianin L) does not show any hydrogen bond interaction with the amino acid residue of human G9a-like protein lysine Methyltransferase (hPKMT) as shown in Figure 1c.

DISCUSSION

Artocarpus heterophyllus (AH) is one among the nine *Artocarpus* species reported from India, which belongs to mulberry (Moracaea) family (Rao *et al*., 2010). *A. heterophyllus* (AH) is known by various regional names for instance i) Jackfruit (English), ii) Palaa (Tamil), iii) Phanas (Gujarati and Marathi) and iv) Chakka (Malayalam). *A. heterophyllus* (AH) is native to Western Ghats of India, Malaysia and also found in Central and Eastern Africa (Prakash *et al*., 2009). Traditionally *A. heterophyllus* (AH) is used to treat diabetes, diarrhea, inflammation, malarial fever, and tape worm infections. Moreover, Artoindonesianin F has been isolated from *A. heterophyllus* and reported to inhibit tyrosinase activity (Rao *et al*., 2010). Furthermore, Artoindonesianin F has been reported to inhibit human Neutrophil Elastase (hNE) using molecular docking method (Narayanaswamy *et al*., 2013). Thus,

Table 1: Toxicity analysis of 17 chosen Artoindonesianins (ligands) using the pkCSM online server.

Ligands	AMES[a]	MTD[b]	hERG I[c]	hERG II[d]	ORAT[e]	ORCT[f]	HT[g]	SS[h]	MT[i]
Artoindonesianin A	No	0.175	No	Yes	2.515	1.859	No	No	-0.609
Artoindonesianin B	No	0.143	No	Yes	2.903	1.952	No	No	1.23
Artoindonesianin B1	Yes	0.378	No	Yes	2.372	0.867	No	No	0.36
Artoindonesianin C	No	-0.209	No	Yes	1.959	2.038	Yes	No	1.341
Artoindonesianin E1	No	-0.165	No	Yes	2.246	1.505	No	No	-0.07
Artoindonesianin J	No	0.299	No	Yes	2.782	1.253	No	No	-0.616
Artoindonesianin L	No	0.488	No	Yes	2.571	2.619	No	No	-0.375
Artoindonesianin N	No	0.387	No	Yes	2.14-3	1.57	No	No	-0.144
Artoindonesianin O	No	0.22	No	Yes	2.207	0.808	No	No	0.019
Artoindonesianin P	No	0.472	No	Yes	2.488	2.291	Yes	No	1.022
Artoindonesianin Q	No	0.242	No	Yes	2.282	2.219	No	No	0.365
Artoindonesianin R	No	0.161	No	Yes	2.237	1.642	No	No	1.087
Artoindonesianin S	No	0.159	No	Yes	2.181	2.097	No	No	0.786
Artoindonesianin T	No	0.474	No	Yes	2.447	2.503	No	No	1.178
Artoindonesianin U	No	0.45	No	Yes	2.509	2.855	No	No	-0.748
Artoindonesianin V	No	0.367	No	Yes	2.574	2.675	No	No	-1.026
Artoindonesianin Y	Yes	-0.117	No	Yes	2.473	1.012	No	No	-1.307

Note: AMES[a] –AMES toxicity; MTD[b] –Maximum Tolerated Dose (expressed in log mg/kg/day); hERG-1[c]- Human Ether-a-go-go-Related Gene inhibitor 1; hERG-2[d] Human Ether-a-go-go-Related Gene inhibitor 2; ORAT[e] Oral Rat Acute Toxicity (expressed in mol/kg); ORCT[f]- Oral Rat Chronic Toxicity (expressed in mg per kg_bw/day); HT[g]- Hepato (liver) toxicity; SS[h]- Skin Sensitization; MT[i]- Minnow Toxicity (expressed in log mM).

Table 2: The Swissdock binding energy analysis of 17 chosen Artoindonesianins (ligands) with the human neutrophil elastase (hNE) using Swissdock method.

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°	RMSD** compared with sivelestat docked complex (A°) value
Artoindonesianin A	6.29	NHBI***	-	-	1.74
Artoindonesianin B	7.23	Arg147 Phe192	3.25 2.51	4.07 3.14	1.49
Artoindonesianin B1	7.21	His57 Ser195 Val216	2.29 3.25 2.75	3.22 3.83 3.18	1.32
Artoindonesianin C	7.85	His57 Ser195 Val216	2.79 2.62 2.78	3.15 3.57 3.63	1.08
Artoindonesianin E1	7.15	Asn61 Ser195	2.80 3.23	3.47 3.74	0.78
Artoindonesianin J	7.48	Ser195	2.95	3.38	0.95
Artoindonesianin L	7.55	His57 Asn61	1.90 2.50	2.85 3.19	1.20
Artoindonesianin N	7.00	His57 Ser195	2.32 2.65 and 2.62	3.18 3.35	0.97
Artoindonesianin O	6.92	His57	3.74	4.08	1.27
Artoindonesianin P	7.09	Phe41 Gly193 Val216	2.59 3.13 2.81	2.93 4.06 3.53	0.95
Artoindonesianin Q	7.50	Phe192 Ser195 Ser214	3.27 3.16 1.80	3.70 3.90 2.71	1.53
Artoindonesianin R	7.43	His57 Ser195	2.26 3.16	3.22 3.72	1.09
Artoindonesianin S	7.72	Arg147 Ser195	3.03 3.31 and 3.48	3.98 3.85	1.24
Artoindonesianin T	7.16	Val190 Ser195 Ser195	2.89 3.54 3.52	3.72 3.94 3.94	1.17
Artoindonesianin U	8.03	Phe41 Asn61 Gly193	2.71 3.22 2.89	3.32 3.74 3.80	1.12
Artoindonesianin V	6.59	His57 Ser195 Val216	2.79 2.62 2.78	3.15 3.57 3.63	1.08
Artoindonesianin Y	7.65	His57 Asn61 Ser195	2.79 3.13 3.03	3.31 3.70 3.87	1.52

Sivelestat (Reference compound 1)	7.54	Gly193	3.05	3.91	Nil
Artoindonesianin F(Reference compound 2)	7.61	Phe41 Asn61 Gly193 Ser195	2.04 2.54 2.17 3.18	3.02 3.25 3.03 3.94	1.05

Note: NHBI*** – No hydrogen bond interactions, RMSD** -Root Mean Square Deviation.

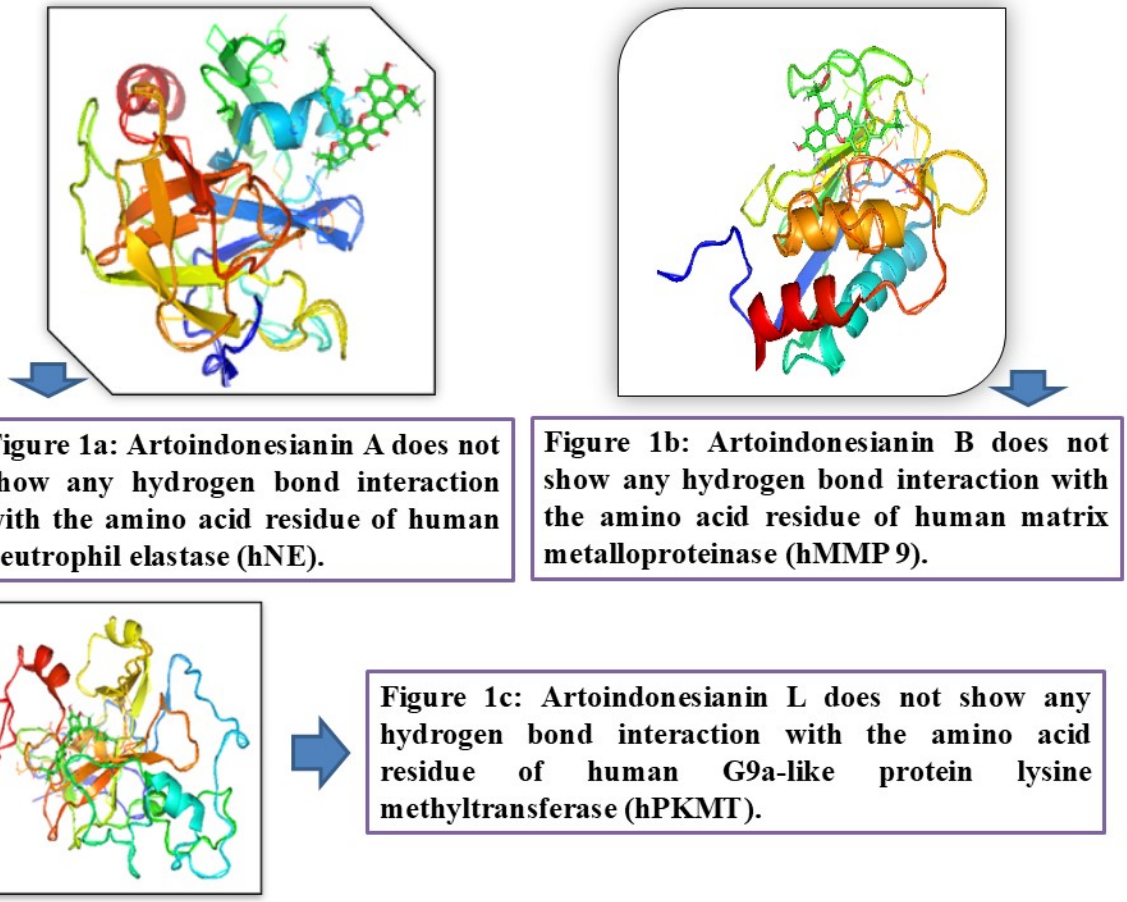

Figure 1: A: Artoindonesianin A does not show any hydrogen bond interaction with the amino acid residue of human neutrophil elastase (hNE). B: Artoindonesianin A does not show any hydrogen bond interaction with the amino acid residue of human matrix metalloproteinase (hMMP 9). C: Artoindonesianin L does not show any hydrogen bond interaction with the amino acid residue of human G9a-like protein lysine Methyltransferase (hPKMT).

in the present study, Artoindonesianin F has been chosen as one of reference compound for human neutrophil elastase (hNE).

Prior to docking, toxicity analysis was carried out in the present study where two (Artoindonesianin C and P) ligands were predicted to possess hepatotoxicity nature. Moreover, Artoindonesianin P has been shown to possess cytotoxicity against P388 (murine leukemia) cells (Hakim *et al.*, 2002). Furthermore, Artoindonesianin U and V have been reported to possess cytotoxicity against P388 (murine leukemia) cells (Syah *et al.*, 2004). However, leaf ethyl acetate fractions of *A. altilis, A. champeden* and *A. heterophyllus* have demonstrated to possess hepatoprotective effect against CCl4 induced liver injury in rat model (Fitrya *et al.*, 2024).

The chosen ligands (Artoindonesianins) have shown interaction with His57, Asn61, Arg147, Gly193 and Ser195 Amino Acid Residues (AAR) of human neutrophil elastase (hNE) enzyme. This finding showed good agreement with previous reports (Mohan *et al.*, 2022, Ragavan *et al.*, 2026).

Similarly selected ligands (Artoindonesianins) have exhibited interaction with Leu188, Ala189, Ala191, Gln227 and Tyr248 Amino Acid Residues (AAR) of human matrix metalloproteinase 9 (hMMP 9) enzyme. This result showed excellent correlation

Table 3: The Swissdock binding energy analysis of 17 chosen Artoindonesianins (ligands) with the human matrix metalloproteinase (hMMP 9) using Swissdock method.

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°	RMSD** compared with caffeic acid docked complex (A°) value
Artoindonesianin A	6.57	Ala191	3.29	3.64	2.68
Artoindonesianin B	7.43	NHBI***	_	_	1.26
Artoindonesianin B1	7.96	Leu188 Ala189 His236 Ala242	2.12 2.48 2.54 3.13	3.05 3.33 3.17 3.93	1.28
Artoindonesianin C	7.46	His236 Tyr248	2.18 2.57	3.08 3.48	1.10
Artoindonesianin E1	6.97	NHBI***	-	-	2.24
Artoindonesianin J	9.11	NHBI***	-	-	0.99
Artoindonesianin L	9.14	Gln227	2.38 and 2.58	3.24 and 3.22	0.89
Artoindonesianin N	7.98	NHBI	-	-	0.79
Artoindonesianin O	7.79	Pro254	2.01	2.75	1.15
Artoindonesianin P	7.75	Gln227 His230 Tyro248	2.41 2.97 2.71	3.25 3.44 3.29	1.04
Artoindonesianin Q	7.81	Leu188 Ala189 Gln227	2.19 2.82 1.88	3.15 3.34 2.82	1.29
Artoindonesianin R	8.11	Leu188 Ala189	2.00 2.30 and 1.99	2.94 3.28 and 2.82	1.37
Artoindonesianin S	7.31	Gln227 Tyr248	3.13 2.58	4.06 3.42	1.61
Artoindonesianin T	7.10	Ala191 Gly233	3.10 2.53	4.06 3.13	1.91
Artoindonesianin U	8.51	Leu188 Ala189 Gln227	2.35 2.90 2.58	3.30 3.753.35	1.68
Artoindonesianin V	8.92	Asp185 Gly186 Tyr218 Tyr248	3.40 2.71 2.18 2.90	3.74 3.55 3.00 3.78	0.94
Artoindonesianin Y	8.20	Leu188 Ala189	2.03 2.33 and 1.93	2.98 3.29 and 2.87	0.95
Caffeic acid (Reference compound 1)	7.08	Glu241 Tyr245	2.73 2.02	3.46 2.99	Nil
Genistein (Reference compound 2)	7.73	Arg249	3.40	3.85	0.58

Note: NHBI*** – No hydrogen bond interactions, RMSD** -Root Mean Square Deviation.

Table 4: The Swissdock binding energy analysis of 17 chosen Artoindonesianins (ligands) with the human G9a-like protein lysine methyltransferase (hPKMT) using Swissdock method.

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°	RMSD** compared with BIX-01294 docked complex (A°) value
Artoindonesianin A	7.61	Ser980 Arg985 Tyr1009] Thr1016	3.55 3.10 3.00 2.87	3.98 4.04 3.91 3.54	4.41
Artoindonesianin B	7.07	Thr1016	2.87	3.54	4.26
Artoindonesianin B1	7.34	Trp1107 Arg1226	3.35 and 2.60 2.20	3.93 and 3.21 3.18	1.03
Artoindonesianin C	7.37	Pro1068 Arg1180	3.38 2.19	3.89 3.10	4.19
Artoindonesianin E1	7.75	Asp1210	3.00	3.84	3.33
Artoindonesianin J	7.41	Arg1101	3.09	4.03	1.62
Artoindonesianin L	7.68	NHBI***	-	-	3.79
Artoindonesianin N	7.89	Trp1107	2.60 and 2.05	3.25 and 2.97	0.95
Artoindonesianin O	7.30	Tyr1211	2.40	2.96	1.03
Artoindonesianin P	7.74	His1170 Arg1226	2.16 2.52 and 3.08	3.08 3.45 and 3.55	1.02
Artoindonesianin Q	8.72	Met1105 Ser1141 Arg1226 Cys1227	2.75 1.86 2.27 3.47	3.66 2.74 3.03 3.84	1.13
Artoindonesianin R	8.41	Arg1166 Ser1224 Arg1226	1.96 2.01 2.06	2.85 2.89 3.03	1.05
Artoindonesianin S	7.81	Asp1145 Asp1210 Arg1214	2.02, 2.01, 2.13 2.73 3.10	2.89, 2.89, 3.10 3.14 3.62	2.63
Artoindonesianin T	8.35	Arg1101 Try1107 Tyr1142 Arg1166 Ser1224 Arg1226	3.05 2.73 2.60 2.61 2.88 2.32	3.79 3.69 3.43 3.27 3.65 3.25	1.00
Artoindonesianin U	9.28	Trp1107 Ser1141 Tyr1142 Asn1169	2.99 and 2.63 2.90 2.72 2.03	3.70 and 3.50 3.64 3.13 3.00	1.38
Artoindonesianin V	6.61	His1076	2.55	2.96	7.36
Artoindonesianin Y	7.93	Pro1068	2.47	2.90	3.87

BIX-01294 (Reference compound 1)	8.12	Arg1101 Trp1107 Ser1141	2.69 3.15 2.83	3.54 4.08 3.72	Nil
MS8511(Reference compound 2)	7.71	Arg985 Ser1005 Tyr1009	3.24 3.52 3.17	3.94 3.86 4.08	3.33

Note: NHBI*** – No hydrogen bond interactions, RMSD** -Root Mean Square Deviation.

with earlier reports (Ragavan *et al*., 2020, Radhakrishnan *et al*., 2023, Ragavan *et al*., 2026).

In the present study, one ligand (Artoindonesianin S) has shown interaction with Asp1145 and Arg1214 Amino Acid Residues (AARs) of human G9a-like protein lysine methyltransferase (hPKMT). This finding was on par with the previous reports (Zang *et al*., 2017, Rahman *et al*., 2021).

CONCLUSION

In the current investigation, the 17 chosen Artoindonesianins of *Artocarpus* species have shown the potential to dock with three targeted human enzymes (hNE, hMMP 9 and hPKMT). However, one ligand (Artoindonesianin A) does not show any hydrogen bond interaction with the amino acid residue of Human Neutrophil Elastase (hNE). Moreover, three ligands (Artoindonesianin B, E1 and J) do not show any hydrogen bond interaction with the amino acid residue of Human Matrix Metalloproteinase (hMMP 9). Furthermore, one ligand (Artoindonesianin L) does not show any hydrogen bond interaction with the amino acid residue of human G9a-like protein Lysine Methyltransferase (hPKMT). Thus, the present finding give new insight about the 17 chosen Artoindonesianins of *Artocarpus* species as potent modulating agents of hNE, hMMP 9 and hPKMT which will help in managing cancer, inflammation, photo-aging, and wounds.

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ABBREVIATIONS

AAR: amino acid residues; **AH:** *Artocarpus heterophyllus;* **hERG:** Human ether-a-go-go-related gene; **hNE:** Human neutrophil elastase; **hMMP 9:** Human matrix metalloproteinase 9; **hPKMT:** Human G9a-like protein lysine methyltransferase; **HT:** Hepatotoxicity; **CID:** Compound Identifier; **2D:** Two dimensional; **3D:** Three dimensional; **PDB:** Protein Data Bank; **HBE:** Highest binding energy; **LBE:** Least binding energy; **MBE:** Maximum binding energy; **MT:** Minnow toxicity; **MTD:** Maximum tolerated dose; **NHBI:** No hydrogen bond interactions; **ORAT:** Oral rat acute toxicity; **ORCT:** Oral rat chronic toxicity; **PLIP:** Protein-ligand interaction profiler; **RMSD:** Root mean square deviation; **SS:** Skin sensitization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, H.R.D., R.N.; methodology, H.R.D., R.N.; software, H.R.D., R.N.; formal analysis, H.R.D., S.B.S., B.D., R.N.; investigation, H.R.D., S.B.S., B.D., R.N.; resources, H.R.D., R.N.; data curation, H.R.D., S.B.S., B.D., R.N.; visualization, H.R.D., S.B.S., B.D., R.N.; supervision, R.N.; project administration, H.R.D., R.N.; writing-original draft preparation, H.R.D., S.B.S., B.D., R.N.; writing-review and editing, H.R.D., S.B.S., B.D., R.N.; All authors have read and agreed to the published version of the manuscript.

SUMMARY

In the current study, 17 chosen Artoindonesianins of *Artocarpus* species were studied on the docking behaviour of Human Neutrophil Elastase (hNE), Human Matrix Metalloproteinase 9 (hMMP 9) and human G9A like protein Lysine Methyl Transferase (hPKMT) by using the Swiss dock approach. The docking analysis showed that Artoindonesianin L (hMMP 9) and Artoindonesianin U (hNE and hPKMT) of *Artocarpus* species has exhibited the maximum binding energy (-9.14, -8.03 and -9.28 kcal/mol) with the hMMP 9, hNE, and hPKMT respectively.

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