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IN-SILICO ANALYSIS OF MTA1 AS DRUG TARGET AGAINST NATURAL ANTIOXIDANTS

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ABSTRACT: The protein MTA1 with histone deacetylase activity is a member of the nucleosome remodeling complex encoded by the mta1 gene is frequently overexpressed in biologically aggressive epithelial neoplasms. MTA1 is a nuclear co-regulatory molecule that is highly expressed in many cancers and correlates with tumor metastasis and progression. MTA1 alters signaling events in the tumor micro-environment. MTA1 contributes to cancer progression, may serve as a biomarker and therapeutic target for cancer. The main objective of this study is to perform *in-silico* docking studies and energy minimizations for active sites of mutated MTA1 protein by selecting different naturally available antioxidant molecules in foods to facilitate ligand-binding site interactions and identify the best from the selected ligands.

INTRODUCTION: Phenotypic changes resulted from the dysregulation of genetic and epigenetic processes, including aberrant transcription of genes driven by cell survival, proliferation, immunologic functions, invasion, and metastasis is cancer [1]. Sequence-specific transcription factors and associated coregulatory proteins enable highly ordered but dynamic gene transcription [2]. Coregulators control transcription factor-dependent gene expression through direct binding to transcription factors and indirectly by interacting with his tones and thereby regulating the accessibility of transcription factor to DNA, resulting in the stimulation or repression of the transcription of specific genes [3].

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The overexpressed oncogene in human cancer is c-myc [4] encoding c-MYC, a transcription factor that regulates the expression of downstream target genes and their expressed proteins mediate the biological activities of c-myc [5, 6]. Only partial elucidation of these downstream targets was documented with c-MYC-mediated transformation [7, 8, 9].

These targets include the genes encoding the enzymes lactate dehydrogenase-A (LDH-A) and ornithine decarboxylase (ODC). Genetic evidence suggests a strict requirement in the MYC transformation pathway for both LDH and ODC [7, 8, 9]. Metastasis-associated protein (MTA1) is encoded by mta1 gene in humans and is the first member of the *mta* family genes [10, 11]. The transforming activity of c-MYC is played by an essential effect or mta1 gene. The metastasis-associated 1 (MTA1) protein [10, 12] is representative of a protein family highly conserved through evolution, which also includes the metastasis-associated 1-like protein (MTA1) [13], MTA2 [14,] and MTA3 [15].

MTA1 is a crucial regulator of the metastatic process in both human and rodent mammary tumors [16, 17]. The *mta1* gene was identified to screen for genes expressed in metastatic cells, specifically, mammary adenocarcinoma cell lines and in many other tumor types as well [18, 19, 20, 21]. MTA1 can be correlated with the metastatic potential of at least two types of carcinomas, although it is also expressed in many normal tissues. The role it plays in metastasis is unclear. It was initially thought to be the 70kD component of a nucleosome remodeling deacetylase complex, NuRD, but it is more likely that this component is a different but very similar protein [22. 23, 24, 25]. These two proteins are so closely related, though, that they share the same types of domains. These domains include two DNA binding domains, a dimerization domain, and a domain commonly found in proteins that methylate DNA. The profile and activity of MTA1 suggest that it is involved in regulating transcription and that this may be accomplished by chromatin remodeling MTA1 shows homology with several immediate early genes [26, 27], encoding transcription factors involved in cell growth regulation. MTA1 was identified based on its overexpression in metastatic rat breast cancer [28].MTA1 expression as they relate to either the normal or the transformed cellular phenotype, it was shown that, in malignant breast epithelial cells, MTA1 expression is induced by activation of the here gulin/HER2 pathway [29].

From the previous studies on the molecular analysis of *MTA*1 gene, it was clear that the polymorphisms in it had led to various cancers. The present study is aimed at identifying the best antioxidant molecule to target MTA1 protein.

MATERIALS AND METHODS:

MTA1 Protein: The normal MTA1 protein accession number NM_004689.4 encoding metastasis-associated protein MTA1 iso-form MTA1 [Homo sapiens] [30] and three mutant sequences were considered and subjected for multiple sequence alignment using CLUSTAL Omega to identify the variations in the completely determining sequence (CDS). The mutation was similar in all the mutants, and therefore, the mutant MTA1 protein accession number AAH06177 encoding MTA1 protein [Homo sapiens] [31], was considered for further analysis. The sequences were retrieved from the NCBI database (www.ncbi.nlm.nih.gov).

Clustal Omega: Three or more sequences together in a computationally efficient and accurate manner are aligned by Clustal Omega, a multiple sequence alignment programs. Biologically meaningful multiple sequence alignments of divergent sequences are produced. Evolutionary relationships can be seen *via* viewing Cladograms or Phylograms [32].

***In-silico* Three Dimensional Protein Structure Prediction:** The mutated MTA1 protein is not having any predicted 3-Dimentional structure available in PDB (Protein data bank). The normal MTA1 protein has a predicted structure. Then an alternative method for finding the homologous protein, *i.e.,* ab initio modeling, was used. There is an automated server for protein modeling which searches the homologous protein by fold prediction and sequences are modeled with a high degree of accuracy. The generated model was subjected to several repeated cycles of energy minimization using SPDBV software, and the final model was subjected to stereochemical evaluation.

Three-dimensional structure prediction of protein from the amino acid sequence still remains an unsolved problem even after decades of effort. If the target protein has a homolog already solved, the task is relatively easy, and high-resolution models can be built by copying the framework of the solved structure. However, such a modeling procedure does not help answer how and why a protein adopts its specific structure. If structure homologs (occasionally analogs) do not exist or exist but cannot be identified, models have to be constructed from scratch. This procedure, called ab initio modeling, is essential for a complete solution to the protein structure prediction problem; it can also help us understand the physicochemical principle of how proteins fold in nature. Currently, the accuracy of ab initio modeling is low, and the success is limited to small proteins (<100 residues) [30].

Robetta: Robetta provides both ab initio and comparative models of protein domains. Domains without a detectable PDB homolog are modeled with the Rosetta de novo protocol [33, 34].

Comparative models are built from template PDBs detected and aligned using locally installed versions of HHSEARCH/HHpred, Raptor X, and Sparks-X. Alignments are clustered, and comparative models are generated using the Rosetta CM protocol. The procedure is fully automated. Robetta is continually evaluated through CAMEO (server [11]). Robetta is evaluated in the blind benchmarking experiment CASP. Features include an interactive submission interface that allows custom sequence alignments for homology modeling, constraints, local fragments, and more. It can model multi-chain complexes and provides the option for large-scale sampling. It uses the PDB100 template database, which is updated weekly, a co-evolution-based model database (MDB), and also provides the option for custom templates (https://www.bakerlab.org/).

Ligands:

1. Carnosine (B-Alanyl-L-Histidine): Carnosine (beta-alanyl-L-histidine) **Fig. 1** is a natural imidazole-containing compound found in the non-protein fraction of animal-derived foods [35]. It's important for muscle function. Beta-alanine supplements increase the levels of carnosine in muscles. It was hypothesized that carnosine applies these evidently restricting activities by influencing vitality digestion and additionally by protein homeostasis (proteostasis) [36]. Carnosine (10-25 mM) is capable of inhibiting the catalysis of linoleic acid and phosphatidylcholine liposomal peroxidation (LPO) by the O_2-dependent iron-ascorbate and lipid-peroxyl-radical-generating linoleic acid 13-monohydroperoxide (LOOH)-activated hemoglobin systems, as measured by the thiobarbituric-acid-reactive substance. Carcinine is a good scavenger of OH radicals, as detected by iron-dependent radical damage to the sugar deoxyribose. This suggests that carnosine is able to scavenge free radicals or donate hydrogen ions [37]. Due to the combination of weak metal chelating (abolished by EDTA), OH, and lipid peroxyl radicals scavenging, reducing activities to liberated fatty acid and phospholipid hydroperoxides, carnosine appear to be physiological antioxidants able to efficiently protect the lipid phase of biological membranes and aqueous environments [38]. The cell reinforcement system of carnosine is credited to its chelating impact against metal particles, superoxide dismutase (SOD) - like movement, and ROS and free radicals searching capacity [39]. It represses the development of tumor cells and shows cancer prevention [40].

2. Pelletierine: Pelletierine **Fig. 1** is an alkaloid that is most commonly found in a pomegranate fruit [41]. This compound usually is a citraconoyl group and has a total molecular weight of 141.21 g/mol, whose chemical formula is $C_8H_{15}NO$. And also, most importantly, Pelletierine has an antioxidant activity, which makes it suitable to prevent, inhibit and control the activity of cancer development and progression. In fact, its anticancer properties make Pelletierine acts effectively in the intervening cell cycle, tumor proliferation, invasion and angiogenesis. It is also known to play a major role in clinical applications of other diseases that involves chronic inflammation [42]. Pelletierine has been appeared to eliminate free radicals and decline macrophage oxidative stress and lipid peroxidation in living organisms such as animals and increment plasma cell reinforcement limit in old aged people due to its antioxidant activity [43].

3. (R)-Amygdalin: (R)-Amygdalin **Fig. 1** is a cyanogenic glucoside whose chemical formula is $C_{20}H_{27}NO_{11}$ and molecular weight is 457.4 g/mol derived from the aromatic amino acid phenylalanine. [44]. It is most commonly found in almonds and Rosaceae family seeds particularly the genus *Prunus*, Poaceae (grasses), Fabaceae (legumes), and in other food plants, including flaxseed and manioc. Within these plants, amygdalin and the enzymes necessary to hydrolyze it are stored in separate locations so that they will mix in response to tissue damage. This provides a natural defense system [45]. Amygdalin is rich in stone fruit kernels, such as almonds, apricot (14 g/kg), peach (6.8 g/kg), and plum (4-17.5 g/kg depending on variety), and also in the seeds of the apple (3 g/kg) [46]. Apoptosis is a central process activated by amygdalin in cancer cells. It is suggested to stimulate the apoptotic process by upregulating the expression of Bax (proapoptotic protein) and caspase-3 and downregulating expression of Bcl-2 (anti-apoptotic protein). It also promotes the arrest of the cell cycle in G0/G1 phase and decreases the number of cells entering S and G2/M phases. Thus, it is proposed to enhance the deceleration of the cell cycle by blocking cell proliferation and growth [47].

Amygdalin is well known for its antineoplastic activity by inducing cell programmed death, which in turn makes this suitable as an anticancer drug but not as a cancer treatment [48].

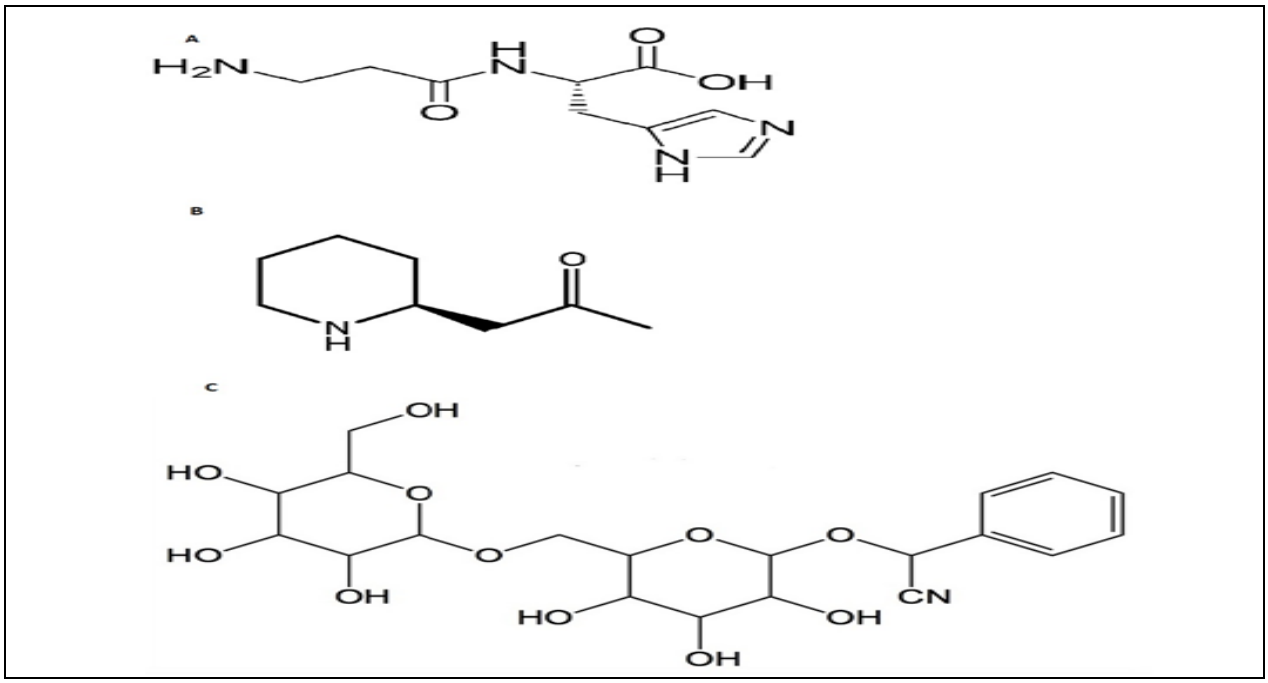

FIG. 1: 2D CHEMICAL STRUCTURE OF A. B-ALANYL-L-HISTIDINE., B. PELLETIERINE., C.(R)-AMYGDALIN DOCKING USING AUTODOCK VINA

Docking using AutoDock Vina: All molecular docking studies were performed using a model for MTA1. To enable the docking, coordinates and parameters were obtained from ChemSpider and the protein and ligands were converted to PDBQT (Vina executable) files, *via* AutoDockTools (v1.5.6) [47]. A grid box centred on the approximate geometric midpoint of the MTA1 with dimensions 36 × 20 × 20 (Å) was assigned as the search region for AutoDock Vina molecular docking software [48]. The exhaustiveness of the search was manually set to 128, all other parameters being the default, to find the most energetically favourable poise. Visual inspection of the PDBQT output files was accomplished using PyMOL© (Schrodinger, LLC) [49].

The exhaustiveness of the search was manually set to 128, all other parameters being the default, to find the most energetically favorable poise. Visual inspection of the PDBQT output files was accomplished using PyMOL© (Schrodinger, LLC) [49].

RESULTS AND DISCUSSION:

Mta1 Protein: The normal MTA1 protein accession number NM_004689.4 and the mutant MTA1 protein accession number AAH06177 encoding MTA1 protein [Homo sapiens] were considered by performing BLASTP of NCBI. The mutant MTA1 protein was 99.16 percent, similar to the normal MTA1 protein.

Normal Sequence: >NP_004680.2 metastasis-associated protein MTA1 iso-form MTA1 [Homo sapiens] MAANMYRVGD YVYFENSSSNPYL IRRIEELNKTANGNVEAKVVCFYRRRDISSTLI ALADKHATLSVCYKAGPGADNGEEGEIEEEM ENPEMVDLPEKLKHQLRHRELFLSRQLESLPA THIRGKCSVTLLNETESLKSYLEREDFFFYSLV YDPQQKTLLADKGEIRVGNRYQADITDLLKE GEEDGRDQSRLETQVWEAHNPLTDKQIDQFL VVARSVGTFARALDCSSSVRQPSLHMSAAAA SRDITLFHAMDTLHKNIYDISKAISALVPQGG PVLCRDEMEEWSASEANLFEEALEKYGKDFT DIQQDFLPWKSLTSIIEYYYMWKTTDRYVQQ KRLKAAEAESKLKQVYIPNYNKPNPNQISVN NVKAGVVNGTGAPGQSPGAGRACESCYTTQ SYQWYSWGPPNMQCRLCASCWTYWKKYGG LKMPTRLDGERPGPNRSNMSPHGLPARSSGS PKFAMKTRQAFYLHTTKLTRIARRLCREILRP WHAARHPYLPINSAAIKAECTARLPEASQSPL VLKQAVRKPLEAVLRYLETHPRPPKPDPVKS VSSVLSSLTPAKVAPVINNGSPTILGKRSYEQ HNGVDGNMKKRLLMPSRGLANHGQARHMG

PSRNLLLNGKSYPTKVRLIRGGSLPPVKRRRM NWIDAPDDVFYMATEETRKIRKLLSSSETKR AARRPYKPIALRQSQALPPRPPPPAPVNDEPIV IED

Mutant Sequence: >AAH06177.1 MTA1 protein [Homo sapiens] MKTRQAFYLHTTKLTRIAR RLCREILRPWHAARHPYLPINSAAIKAECTAR LPEASQSPLVLKQAVRKPLEAVLRYLETHPRP PKPDPVKSVSSVLSSLTPAKVAPVINNGSPTIL GKRSYEQHNGVDGNMKKRLLMPSRGTYLGL ANHGQTRHMGPSRNLLLNGKSYPTKVRLIRG GSLPPVKRRRMNWIDAPDDVFYMATEETRKI RKLLSSSETKRAARRPYKPIALRQSQALPPRPP PPAPVNDEPIVIED By using CLUSTAL Omega, multiple sequence alignment of both normal MTA1 protein sequence and the mutant MTA1 protein was carried out. The results showed an insertion of four amino acids, "TYLG" after 605 amino acid residue of the normal protein. The same was noticed in all the mutant sequences retrieved from the NCBI database. Henceforth, this mutant MTA1 protein accession number AAH06177 encoding MTA1 protein [Homo sapiens] was utilized in all the further analysis **Fig. 2**.

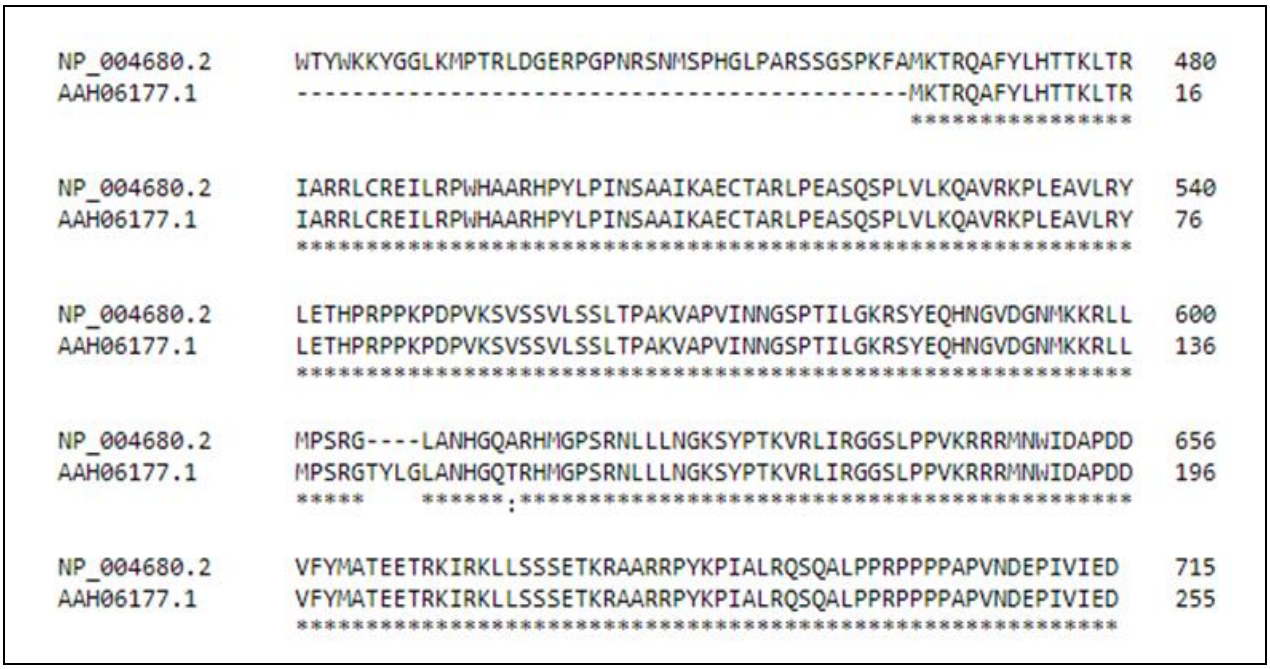

FIG. 2: MULTIPLE SEQUENCE ALIGNMENT OF NORMAL AND MUTANT MTA1 PROTEIN SEQUENCES USING CLUSTAL OMEGA

AbInitio Modeling: The mutated MTA1 protein, which encodes for the metastatic tumor-associated protein, has no 3-Dimentional structure available in PDB (Protein databank), as the 3-Dimentional structure was not elucidated either by using X- ray crystallographic or NMR studies.

The protein sequence was subjected to pBLAST at NCBI and was analyzed by multiple sequence alignment. Then an alternative method for finding the homologous protein, *i.e.*, ab initio modeling, was used. There is an automated server for protein modeling which searches the homologous protein by fold prediction, and sequence was modeled with high degree of accuracy using ROBETTA. The generated model was subjected to several repeated cycles of energy minimization using SPDBV software, and the final model was subjected to stereochemical evaluation **Fig. 3**.

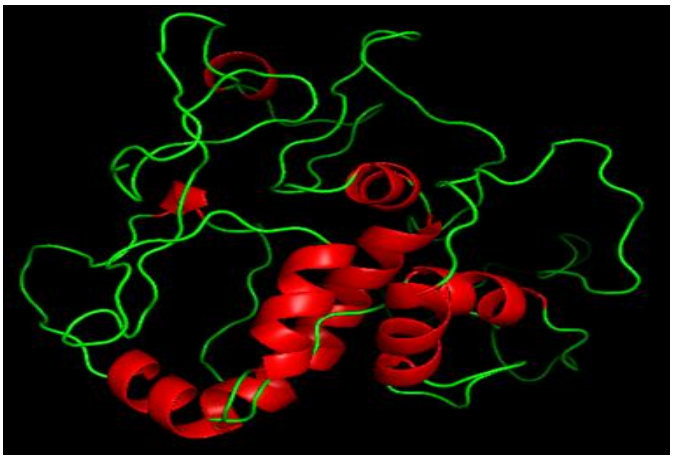

FIG. 3: AB INITIO MODELLED STRUCTURE OF MUTATED MTA1

Protein-Ligand Interactions: Using Auto Dock Vina software, protein-ligand interaction studies carried out by performing energy minimizations to identify the best ligand that interacts with the modeled structure of mutant MTA1 protein at minimal energy states. Each ligand interaction with the mutant MTA1 protein were carried out for 20 folds to attain the minimal energy state. Out of the three ligands (R)-Amygdalin was the best with a minimal energy of -8.0 k. cal/mol.

The other two ligands, β-alanyl-L-histidine and Pelletierine were also effective against MTA1 with -4.9 k. cal/mol and -3.7 k.cal/mol binding energy.

TABLE 1: MINIMAL ENERGY STATES OF PROTEIN-LIGAND INTERACTIONS

S. no.	Ligand	Emergy (k.cal/mol)
1	Carnosine (β-alanyl-L-histidine)	-4.9
2	Pelletierine	-3.7
3	(R)-Amygdalin	-8.0

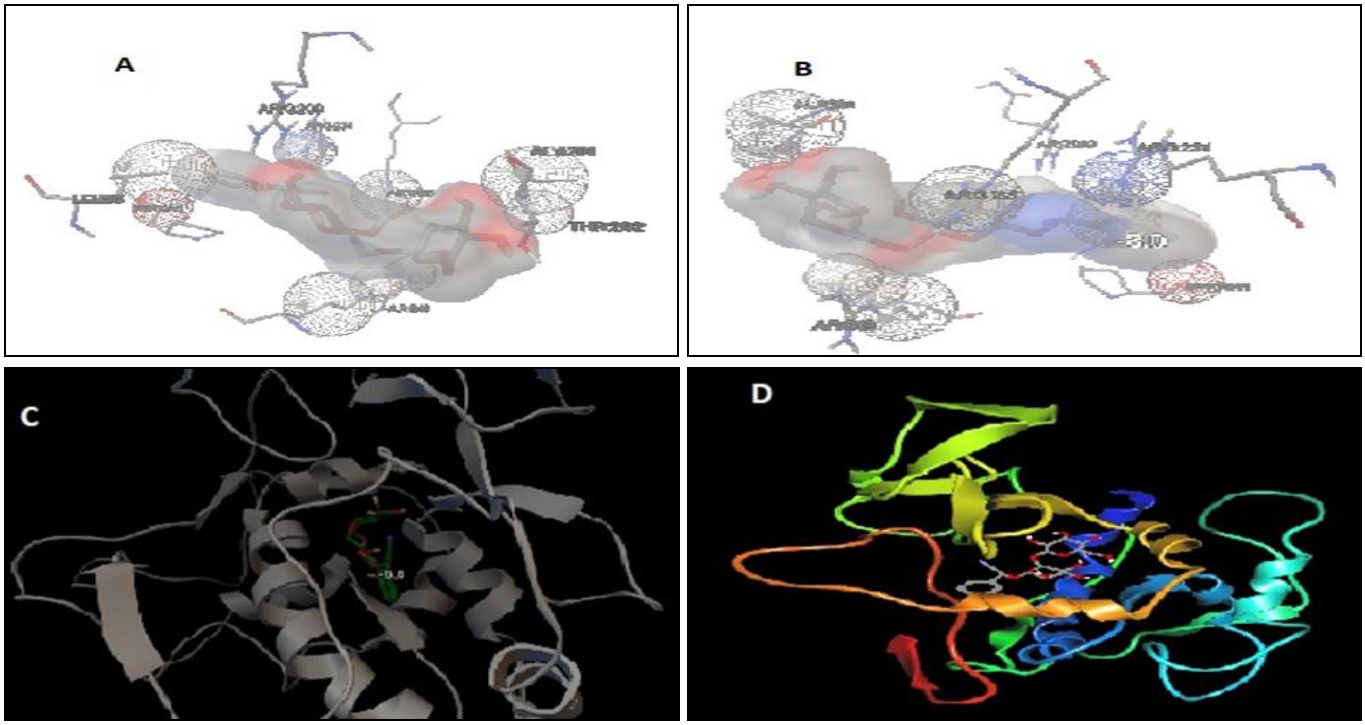

FIG. 4: BINDING OF R-AMYGDALIN WITH MUTANT MTA1

DISCUSSION: It would be of interest to extend our docking studies to other drugs and to look at reconciling the functional effects observed with mutated MTA1 *in-silico*.

This requires solvating the MTA1 model prior to any docking studies. Such work is beyond the scope of the current investigation, but our docking with MTA1 permits comparison to other recent studies describing binding sites in MTA1.

CONCLUSION: It was concluded that (R)-Amygdalin was the best ligand as it showed minimal energy when compared with the other two, and therefore the metastatic progression by MTA1 can be minimized.

The other two ligands, β-alanyl-L-histidine and Pelletierine were also effective against MTA1. Recent studies have shown that amygdalin can kill cancer cells in certain cancer types; there is no enough reliable scientific evidence to show that amygdalin can treat cancer. Despite this, it still gets promoted as an alternative cancer treatment. The current work epitomizes complete inter-pretations about all known anti-cancer mechanisms of amygdalin, the possible role of naturally occurring amygdalin in fight against cancer and mistaken belief about cyanide toxicity causing the potential of amygdalin. However, well-planned clinical trials are still needed to be conducted to prove the effectiveness of this substance *in-vivo* and to get approval for human use. Antioxidants are chemicals that interact with and neutralize free radicals, thus preventing them from causing damage. Antioxidants are also known as “free radical scavengers.”

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CONFLICTS OF INTEREST: This statement is to certify that all authors have seen and approved the manuscript being submitted. We warrant that the article is the Authors' original work. We warrant that the article has not received prior publication and is not under consideration for publication elsewhere. On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission.

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