

## In silico design of a drug from the compounds that are suggestive in the treatment of arsenicosis using molecular docking

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### ABSTRACT

In our quest to find a cure for arsenicosis, an in silico attempt was made to identify a common target for the compounds that relieves the symptoms using Autodock and Discovery studio. Retinol, alpha-tocopherol, ascorbic acid, alpha-lipoic acid and folic acid were used as ligands and an enzyme telomerase reverse transcriptase which was selected as the target protein to search for the structure which had the highest binding affinity with this cancer causing enzyme of the human body. This compound was compared with other potential inhibitors currently under research by docking with 47 important enzymes of the human body found in the protein data bank. Assessment by FAF-Drugs web server showed this compound to be non-toxic. To prove the effectiveness of this drug, both in vivo and in vitro studies are required along with this in silico study.

**Keywords:** Quinazolin-4-one, GABA (A) R-beta3 homopentamer, Molecular docking

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### INTRODUCTION

Cancer of skin along with cancer of some internal organs- liver, kidney, urinary bladder is not uncommon [1] in arsenicosis. Patients once affected may not recover even after remediation of the arsenic contaminated water. Several vitamins and minerals such as vitamin A [2], ascorbic acid [3], alpha-tocopherol [4], zinc [5], folic acid [6], alpha-lipoic acid [7], and selenium [8] used either alone or in combination were found to be effective in arsenicosis. Some of our foodstuffs such as corn [9], spinach [10], garlic oil [11] and spirulina [12] were proven to relieve the symptoms of arsenicosis. It is still unknown where these compounds act inside the body. The active ingredient inside the foodstuffs responsible for the relief of symptoms is still not identified. The compounds retinol and alpha-tocopherol have specific proteins to which they bind in the serum. But there are no transport proteins for ascorbic acid, folic acid and alpha-lipoic acid. These compounds along with zinc and selenium may have an antioxidant effect in mitigating the oxidative stress produced by excessive arsenic in the body. This study has been undertaken to identify the sites where these compounds function and to recognize a common location where one drug designed from these compounds works.

Although modeling techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, lack of side effects, etc., that first must be optimized before a ligand can become a safe and efficacious drug. These other characteristics are often difficult to optimize using rational drug design techniques. In addition, these drugs should also be designed so as not to affect any other important “off-target” molecules or antitargets that may be similar in appearance to the target molecule, since drug interactions with off-target molecules may lead to undesirable side effects. Sequence homology is often used to identify such risks. Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.

As experimental methods such as X-ray crystallography and NMR develop, the amount of information concerning 3D structures of biomolecular targets has increased dramatically. In parallel, information about the structural dynamics and electronic properties about ligands has also increased. This has encouraged the rapid development of the structure-based drug design. Current methods for structure-based drug design can be divided roughly into two categories. The

first category is about “finding” ligands for a given receptor, which is usually referred as database searching. In this case, a large number of potential ligand molecules are screened to find those fitting the binding pocket of the receptor. This method is usually referred as ligand-based drug design. The key advantage of database searching is that it saves synthetic effort to obtain new lead compounds. Another category of structure-based drug design methods is about “building” ligands, which is usually referred as receptor-based drug design. In this case, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures, not contained in any database, can be suggested [13,14].

In contrast to traditional methods of drug discovery, which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value. Once a suitable target has been identified, the target is normally cloned and expressed. The expressed target is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.

## MATERIALS AND METHODS

### Softwares

a. *Discovery Studio 3.5*

b. *Auto-dockVina*

c. *Marvin Sketch 6.1, 2013, Chem-Axon (<http://www.chemaxon.com>)*

d. *Online software tools:*

i. *BLAST [2],*

ii. *ClustalW2,*

iii. *FAF- Drugs web-server [1]*

### Molecular docking

Alpha-tocopherol was modified using discovery studio 3.5 to 289 structures and in silico docking study was done with the target protein using Auto-dock Vina to identify the structure with highest binding affinity. Naming of the compounds was done by Marvin Sketch 6.1, 2013, Chem-Axon.

### Assessment of toxicity

Assessment of toxicity was done by FAF-Drugs web-server.

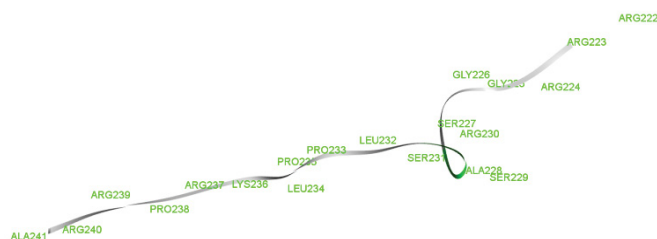
### Comparison of the ligand with other inhibitors

This structure was compared with 11 other compounds to see the interaction with 47 important enzymes of the human body using Auto-dock Vina.

## RESULT

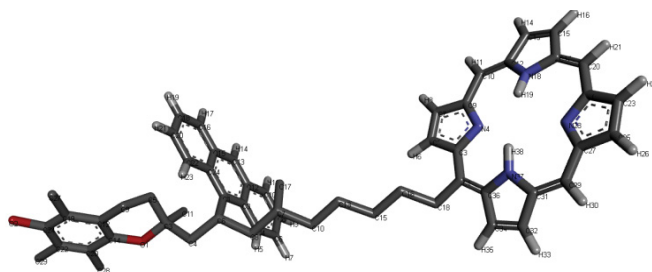
The enzyme reverse transcriptase was searched in protein data bank website and the results revealed 382 proteins of different species among them 53 proteins were associated with Homo sapiens. The first structure to arrive was the crystal structure of human Importin alpha 5 with TERT (Telomerase Reverse Transcriptase) NLS (Nuclear Localisation Sequence) peptide with PDB ID 4B18 released on 4th of September 2013. The structure was predicted using X-Ray diffraction with resolution of 2.52 Å. The compound had two polymers. The first molecule was importin subunit alpha-1 which is a protein with 447 amino acids isolated from Homo sapiens. The second molecule was telomerase reverse transcriptase which was also a protein with 20 amino acids isolated from Homo sapiens. After downloading this protein, it was observed that although in the website it indicated that the fragment consists of residues from 222-240 but when visualizing the protein, it showed that 4 amino acids from 225-228 were absent. So to complete the protein structure, the crystal structure of human Importin alpha 5 with TERT NLS peptide was searched in protein database of PubMed, the FASTA format of this protein was found and missing amino acids were inserted using discovery studio.

The 3D structure of telomerase reverse transcriptase is shown in Figure 1:

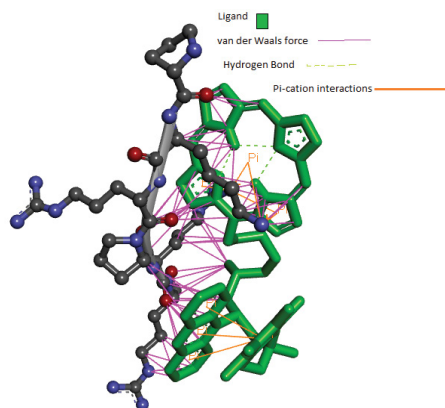


**Figure 1:** 3D structure of telomerase reverse transcriptase showing amino acid residues.

The amino acid sequence of telomerase reverse transcriptase is RRRGGSASRSLPLPKRPRRA. Alpha tocopherol was modified into 289 structures and compound 214 showed the highest binding affinity with a binding energy of -7.5 Kcal/mol Figures 2 and 3.



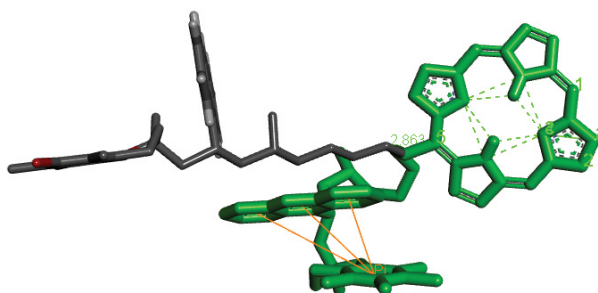
**Figure 2:** Structure of compound 214 showing carbon atoms.



**Figure 3:** Compound 214 binding with telomerase reverse transcriptase by Vanderwaals forces and pi-cation interactions.

#### Assessment of toxicity

Toxicity was assessed using FAF-Drugs web server which revealed that the drug is non-toxic Figure 4.



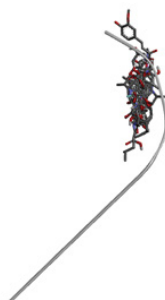
**Figure 4:** The bounded compound 214 when superimposed with the starting molecule on porphyrin rings also shows pi-pi interactions (yellow lines) between the aromatic ring and the anthryl group in 6th position and formation of hydrogen bonds (green dotted line) within the porphyrin ring.

**Comparison of compound 214 with other telomerase reverse transcriptase inhibitors currently under research**

The Table 1 and Figure 5 shows that compound 214 shows the lowest binding energy with telomerase reverse transcriptase compared to other inhibitors currently under research.

Structure	Binding Energy (Kcal/mol)
Epigallocatechin	-4.7
Tretinoin	-4.7
Alterperilenol	-5
Compound 214	-7.5
Curcumin	-4.6
Dideoxyguanosinetriphosphate	-3.7
Genistein	-4.5
Helenalin	-4.9
Isoprenoid	-4
Levofloxacin	-4.8
Ofloxacin	-4.7
Zidovudin	-4.1

**Table 1:** Binding energy of compound 214 and other telomerase reverse transcriptase inhibitors currently under research with telomerase reverse transcriptase.



**Figure 5:** Compound 214 and other inhibitors of telomerase reverse transcriptase binding to telomerase reverse transcriptase at the same site.

**Comparison of compound 214 with other telomerase reverse transcriptase inhibitors currently under research with other important enzymes in the body**

The Tables 2-7 show the interaction of other important enzymes of the body with compound 214 and other inhibitors currently under research.

Enzyme inhibitors	Oxidoreductase enzymes present in the human body (PDB ID)							
	Superoxide dismutase (1HL5)	Catalase (1F4J)	Glutathione S Transferase (2VCV)	Glyceraldehyde 3 Phosphate Dehydrogenase (1ZNO)	Succinate dehydrogenase (2W8R)	Cyt P450 1A1 (4I8V)	Pyruvate dehydrogenase (3EXE)	Aldehyde dehydrogenase (2ONM)
Epigallocatechin	-7.9	-9.2	-7.8	-9.5	-8.1	-7.5	-8.2	No affinity
Curcumin	-7.6	-8.1	-7.7	-8	-7.6	-9.5	-7.9	No affinity
Genistein	-7.2	-9.6	-7.8	-8.3	-7.8	-10.4	-7.9	No affinity
Isoprenoid	-5.1	-6.3	-5.9	-6	-5.9	-5.2	-5.9	-5
Tretinoin	-6.9	-7.8	-7.8	-7	-7.5	-6.9	-7.2	No affinity
Zidovudine	-7.5	-8.6	No affinity	No affinity	-7.2	-7.3	No affinity	No affinity
Ofloxacin	-7.5	-9.2	-8	-7.7	-8.3	-7.3	-8	No affinity
Levofloxacin	-7.9	-8.2	-7.9	-8.5	-8.3	-8.3	-7.3	No affinity
Alterperilenol	-8.2	-10.8	-8.6	-9	-9	-8	-10.1	No affinity
Dideoxyguanosinetriphosphate	-7	-8.6	No affinity	No affinity	-7.5	-7.5	No affinity	No affinity
Helenin	-7.9	-8	-7.7	-17.6	-6.8	-7.4	-7.2	No affinity
Compound 214	-10.2	-11.1	-8.9	-11.1	-10.9	-8.7	-10.8	No affinity

**Table 2:** Binding energy (in kcal/mol) of other inhibitors currently under research compared with compound 214 on oxido-reductases.

Compound 214 has been shown to bind with superoxide dismutase, catalase, glutathione s transferase, glyceraldehyde 3 phosphate dehydrogenase, succinate dehydrogenase, pyruvate dehydrogenase with highest binding affinity compared to other inhibitors currently under research. Though it interacted with Cyt P450 1A1 but its affinity was less than curcumin and genistein. Like other inhibitors it had no affinity with aldehyde dehydrogenase.

Enzyme inhibitors	Transferase enzymes present in the human body (PDB ID)								
	Pyruvate Kinase (1TSF)	DNA Polymerase (3EOJ)	Glucokinase (1V4T)	Phosphoglycerate kinase (3C39)	Acetyl CO-A Acetyl transferase (2F2S)	Serine Threonine Protein Kinase (3I6W)	Phosphatidyl inositol 3 kinase (3CSF)	UDP-N-Acetylglucosamine (3PE3)	Epidermal Growth Factor (3IEI)
Epigallo Catechin	-8.6	-7.3	-7.3	-6.9	-7.5	No affinity	-8.2	-8	-8
Curcumin	-7.9	-7.1	-6.5	-6.7	-6.1	No affinity	-7.3	-7.2	-8.3
Genistein	-8	-7.8	-7.2	-8.3	-6.9	No affinity	-9	-7.2	-8.4
Isoprenoid	-6.7	-6.2	-4.4	-5	-6.2	-5.8	-6.4	-5.5	-5.9
Tretinoin	-8.1	-6.9	-6.4	-7.5	-6.5	No affinity	-7.6	-7.9	-8.4
Zidovudine	-8	-6.9	-6.4	-6.2	-6.9	No affinity	No affinity	No affinity	-7.6
Ofloxacin	-8.4	-8	-7.2	-7.1	-7.3	No affinity	-7.7	No affinity	-7.5
Levofloxacin	-8.7	-7.5	-7.1	-6.9	-7.2	No affinity	-8.1	No affinity	-8.2
Alterperilenol	-8.9	-7.9	-7.6	-8.7	-7.9	No affinity	-10	-8.3	-8.4
Dideoxyguanosinetriphosphate	-9.5	-6.5	-7	-8.6	-6.3	No affinity	No affinity	No affinity	-8.5
Helenin	-8.7	-6.9	-7.3	-6.6	-6.4	No affinity	-7.8	-7.5	-6.8
Compound 214	-8.1	-9.7	-9.4	-10	-9.8	No affinity	-11.1	-9.3	-11.3

**Table 3:** Binding energy (in kcal/mol) of other inhibitors currently under research compared with compound 214 on transferases.

Compound 214 has been shown to bind with DNA polymerase, glucokinase, phosphoglycerate kinase, acetyl CO-A acetyl transferase, phosphatidyl inositol 3 kinase, UDP-N-Acetylglucosamine, epidermal growth factor with highest binding affinity compared to other inhibitors currently under research. Though it interacted with pyruvate kinase but its affinity was less than epigallocatechin, ofloxacin, levofloxacin, alterperilenol, dideoxyguanosinetriphosphate, and helenin. Like other inhibitors it had no affinity with Serine Threonine Protein Kinase.

Enzyme Inhibitors	Hydrolase enzymes present in human body (PDB ID)								
	Tyrosine Phosphatase (2JJJ)	Caspase (3V6M)	Dipeptidyl Peptidase (3CCB)	Ribonuclease (3PUF)	Phosphodiesterase 4D (1MKD)	Sucrase isomaltase (3LPO)	Insulin degrading enzyme (3OFI)	Phosphatidyl inositol Phosphatase (1W8O)	Glutamate Carboxypeptidase (1Z8L)
EpigalloCatechin	-8.1	-8.1	-9.3	No affinity	-8.8	-7.2	-9.2	-7	-9.5
Curcumin	-8	-7.2	-7.8	-6.9	-8.6	-7.5	-8.8	-6.7	-9.3
Genistein	-7.5	-7.6	-9.2	-7.8	-9.3	-6.7	-8.6	-6.8	-8.3
Isoprenoid	-5.1	-6	-5.4	-5.6	-6.9	-5.8	-5.7	-5	-6.1
Tretinoin	-6.2	-6.7	-7.3	No affinity	-8.4	-7.5	-8.6	-6.6	-8.1
Zidovudine	-7	-7.3	-7.7	No affinity	No affinity	-6.4	-7.5	-7.4	-8.2
Ofloxacin	-7.9	-7.2	-7.2	No affinity	No affinity	-7.4	-8.6	-7	-7.8
Levofloxacin	-7.5	-6.9	-8.1	No affinity	No affinity	-7.5	-8	-7	-8.2
Alterperyleneol	-8.1	-8.5	-8.7	No affinity	-10.1	-8.1	-9.8	-7.5	-9.6
Dideoxyguanosinetriphosphate	-7.2	-6.9	-8.1	No affinity	No affinity	-7.9	-8.6	-7	-9.9
Helenin	-7.1	-6.7	-7.3	-7.4	-8.1	-7.2	-7.5	-7.4	-8.8
Compound 214	-10.3	-9.9	-11.6	No affinity	-13.1	No affinity	-10.8	-8.2	-12.8

**Table 4:** Binding energy (in kcal/mol) of other inhibitors currently under research compared with compound 214 on hydrolases.

Compound 214 has been shown to bind with Tyrosine Phosphatase, Caspase, Dipeptidyl Peptidase, Phosphodiesterase 4D, Insulin degrading enzyme, Phosphatidyl inositol Phosphatase, Glutamate Carboxypeptidase with highest binding affinity compared to other inhibitors currently under research. It had no affinity with ribonuclease and sucrase isomaltase.

Enzyme Inhibitor	Lyase enzymes present in human body (PDB ID)							Ferrochelatase (2HRE)
	Enolase (2PSN)	Cyatathionine beta synthase (1JBQ)	UDP glucuronic acid decarboxylase (4LK3)	DNA lyase (3U8U)	Hydroxymethyl glutaryl-CoA lyase (2CW6)	Serine dehydratase (2RKB)	GDP mannose dehydratase (1T2A)	
Epigallocatechin	-7.5	-7.7	-8.8	-8.6	-8.6	-8.6	-8.3	-8.9
Curcumin	-7.7	-6.5	-7.4	-6.8	-8.4	-7.7	-9.6	-8.2
Genistein	-7.3	-7.4	-8.3	-8	-8.3	-7.8	-9.8	-8.5
Isoprenoid	-5.2	-5.5	-5.7	-5.8	-6.6	-6.5	-5.8	-5.8
Tretinoin	-7.7	-7.2	-7	-7.9	-8.8	-8.3	-8.6	-7.4
Zidovudine	-7.3	No affinity	-7.4	-6.8	-7.4	-8.2	-9	-7.8
Ofloxacin	-7.3	-7.5	-7.9	-9	-8.2	-8.4	-8.7	-9.3
Levofloxacin	-7.6	-6.5	-8.7	-8.6	-8.9	-8.7	-9.5	-9
Alterperyleneol	-8.4	-8	-9.3	-8.5	-10	-9.8	-8.4	-10
Dideoxyguanosinetriphosphate	-7.6	No affinity	-9.1	-8.1	-8.5	-9.1	-10	-7.6
Helenin	-7.2	-7.6	-8.5	-7.6	-9.9	-8.3	-8.9	-7.8
Compound 214	-10	-9.8	-10.8	-10.4	-13.3	-12.3	-9.2	-10.2

Table 5: Binding energy (in kcal/mol) of other inhibitors currently under research compared with compound 214 on lyases.

Compound 214 has been shown to bind with Enolase, Cyatathionine beta synthase, UDP glucuronic acid decarboxylase, DNA lyase, Hydroxymethyl glutaryl-CoA lyase, Serine dehydratase and Ferrochelatase with highest binding affinity compared to other inhibitors currently under research. Though it interacted with GDP mannose dehydratase but its affinity was less than curcumin, levofloxacin, dideoxyguanosinetriphosphate, and genistein.

Enzyme inhibitors	Isomerase enzymes present in human body (PDB ID)					
	Glucose 6 Phosphate Isomerase (1JLH)	Triose phosphate isomerase (4BR1)	Protein Phosphatase (2JJD)	Autocrine Motility Factor (1IRI)	Biphospho glycerate mutase (3NFY)	UDP N-Acetyl glucosamine 2 epimerase (3EO3)
Epigallo Catechin	-7.3	-8.7	-8.3	-8.9	-7.4	-4.9
Curcumin	-6.8	-8	-7.7	-7.2	-7.4	-6.7
Genistein	-7.6	-8.5	-8.1	-7.8	-8.2	-6.6
Isoprenoid	-4.7	-5.8	-5.5	-5.3	-5.5	-4.7
Tretinoin	-6.5	-7.5	-7.3	-6.9	-7	-5
Zidovudine	No affinity	-7.8	-8.3	No affinity	-7.2	-4.9
Ofloxacin	No affinity	-7.7	-7.7	-7	-8.3	-4.8
Levofloxacin	No affinity	-7.5	-8.5	-6.7	-8.2	-5.1
Alterperyleneol	-8.4	-7.7	-9.1	-8.4	-8.2	-5.5
Dideoxyguanosinetriphosphate	No affinity	-9	-8.3	No affinity	-8.8	-4.2
Helenin	-7.5	-6.6	-7.6	-7.9	-7	-5.4
Compound 214	-9.9	-7.3	-10	-10.2	-8.3	-6.4

Table 6: Binding energy (in kcal/mol) of other inhibitors currently under research compared with compound 214 on isomerases.

Compound 214 has been shown to bind with Glucose 6 Phosphate Isomerase, Protein Phosphatase, Autocrine Motility Factor and Biphospho glycerate mutase with highest binding affinity compared to other inhibitors currently under research. Though it interacted with Triose phosphate isomerase and UDP N-Acetyl glucosamine 2 epimerase but its affinity was not highest.

Enzyme Inhibitor	Ligase enzymes present in human body (PDB ID)					
	Pyruvate Carboxylase (3BG3)	Glutamine Synthetase (2QC8)	Ubiquitin Protein Ligase (3ZNI)	Baculoviral protein (3CMZ)	DNA ligase (3II6)	Tryptophan t-RNA Synthetase (2AZX)
Epigallo Catechin	-9.4	-8.8	-8.6	-8.2	-8	-9
Curcumin	-8.4	-8.9	-7.4	-7.6	-6.4	-7.2
Genistein	-9.4	-8.6	-9.2	-8.1	-7.5	-8.4
Isoprenoid	-5.1	-6.2	-6.1	-5.7	-5.3	-5.4



<b>Tretinoin</b>	-6.5	-7.9	-8	-7.5	-6.7	-8.5
<b>Zidovudine</b>	No affinity	No affinity	-7.1	-7.6	-7.2	-7.8
<b>Ofloxacin</b>	No affinity	-8.7	-7.7	-8.8	-7.3	-8.8
<b>Levofloxacin</b>	No affinity	-8.7	-7.6	-8.8	-7	-8
<b>Alterperyleneol</b>	-8.9	-9.5	-8.7	-8.9	-7.6	-9.4
<b>Dideoxyguanosinetriphosphate</b>	No affinity	No affinity	-7.3	-7.9	-7.6	-9.9
<b>Helenin</b>	No affinity	-7.9	-7.3	-7.8	-7.5	-8.2
<b>Compound 214</b>	-11.2	-11.2	-9.2	-10.8	-10	-10.9

**Table 7:** Binding energy (in kcal/mol) of other inhibitors currently under research compared with compound 214 on ligases.

Compound 214 has been shown to bind with Pyruvate Carboxylase, Glutamine Synthetase, Ubiquitin Protein Ligase, Baculoviral protein, DNA ligase, Tryptophan t-RNA Synthetase and E3 ligase with highest binding affinity compared to other inhibitors currently under research.

## DISCUSSION

The *in silico* voyage of discovering a cure for arsenicosis resulted in rational designing of a drug which binds with telomerase reverse transcriptase. Telomerases are part of a distinct subgroup of RNA-dependent polymerases. Telomerase lengthens telomeres in DNA strands, thereby allowing senescent cells that would otherwise become postmitotic and undergo apoptosis and become potentially immortal cancerous cells. To be specific, telomerase reverse transcriptase is responsible for catalyzing the addition of nucleotides in a TTAGGG sequence to the ends of a chromosome's telomeres [15]. This addition of repetitive DNA sequences prevents degradation of the chromosomal ends following multiple rounds of replication [16].

Genome-wide association studies suggest telomerase reverse transcriptase is a susceptibility gene for development of many cancers including lung cancer. Telomerase activity is associated with the number of times a cell can divide playing an important role in the immortality of cell lines, such as cancer cells. The enzyme complex acts through the addition of telomeric repeats to the ends of chromosomal DNA. This generates immortal cancer cells [17]. In fact, there is a strong correlation between telomerase activity and malignant tumors or cancerous cell lines [17]. Not all types of human cancer have increased telomerase activity. 90% of cancers are characterized by increased telomerase activity [17]. Lung cancer is the most well characterized type of cancer associated with telomerase.

If increased telomerase activity is associated with malignancy, then possible cancer treatments could involve inhibiting its catalytic component, human telomerase reverse transcriptase, to reduce the enzyme's activity and cause cell death. Since normal somatic cells do not express telomerase reverse transcriptase, telomerase inhibition in cancer cells can cause senescence and apoptosis without affecting normal human cells [17]. Inhibition of telomerase reverse transcriptase led to apoptosis and cell death in cells with short telomere lengths a promising result for cancer treatment [17]. Although cells with long telomeres did not experience apoptosis, they developed mortal characteristics and underwent telomere shortening [17-20].

## CONCLUSION

The findings reveal that if many drugs are proven effective for a disease whose exact molecular pathogenesis is not clearly defined, then those drugs have the possibility of binding to a common target to alleviate the symptoms. This study also suggests the rationality of using these compounds in combination so long as an effective cure is not discovered for arsenicosis. The minerals zinc and selenium may be explored in the future if metal docking softwares are developed. Identification of active compounds in the food stuffs proven to be effective in this condition and their *in silico* analysis may disclose more insights in this field. The potential areas of *in silico* intervention in the drug discovery process expose endless possibilities and opportunities for research at a molecular level.

## DECLARATION

### *Availability of data and materials*

The data supporting findings can be found within the manuscript.

**Author contributions**

None of the authors have any competing interests. Tarek Golam Mustafa Mohammad conceived of the presented idea, developed the theory performed the computations and verified the analytical methods. Mir Misbahuddin encouraged Tarek Golam Mustafa Mohammad to investigate and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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