Original Article
Cite This: Colloid & Nanoscience Journal 2(3) (2025) 382-389.
CNJ.araku.ac.ir

The effect of gold nanoparticles on the inhibition of BCR-ABL protein as a leukemia factor using molecular docking method

Mohammad Mohammad Ali Mansouri[1]*, Motahhareh Hemmati Nasab[1], Masoumeh Karim Pour[1], Mehdi Rezvani Mehr[1]

Received: 2025-01-18
Revised: 2025-02-10
Accepted: 2025-02-13
DOI: 10.61186/CNJ.2.3.382

[1]Department of Biology, Faculty of Science, University of Shahid Chamran, Ahvaz, Iran

Abstract

Blood cancer, also known as leukemia, is a type of cancer that affects blood cells and bone marrow, leading to abnormal production of blood cells. It is one of the most common types of cancer in children and adults, and its prevalence has increased in recent years, so that in some regions, leukemia has emerged as a public health challenge and has increased the need for attention and targeted treatments. The BCR-ABL protein, which is known as an oncogene, plays a key role in the pathogenesis of chronic myeloid leukemia. This paper investigates the molecular docking of gold nanoparticles on the BCR-ABL protein as an effective agent in the treatment of leukemia. In this study, schrodinger PyMOL 2.5.5 software was used to perform molecular docking. The gold nanoparticles and BCR-ABL protein molecules were designed and extracted using the RCSB and PubChem databases. The nanoparticles were placed at random distances and different orientations relative to the protein, and the docking simulation was repeated 50 times to determine the key interaction points. The results show that gold nanoparticles are able to successfully dock with the BCR-ABL protein. This interaction is achieved by hydrogen bonds, electrostatic interactions, and van der Waals forces. The findings suggest that gold nanoparticles can act as an effective inhibitory agent in the treatment of leukemia by targeting the BCR-ABL protein, and further research is needed to evaluate the clinical effects of these nanoparticles in targeted therapies.

Keywords: Bioinformatics, Gold nanoparticles, Molecular Docking Simulation, Leukemia

1. Introduction

Chronic myeloid leukemia is a chronic myeloproliferative disease caused by a specific mutation in the multipotent stem cells of the bone marrow. The prevalence of this disease in the world is reported to be 2 to 3 people per 100,000 people per year [1]. The dependence of this disease on genetic factors was reported by Rowley in 1973 [2]. He identified the presence of an abnormal Philadelphia chromosome as one of the factors for the occurrence of CML in patients. In 1980, it was determined that the Philadelphia chromosome is the result of the connection of the ABL gene on chromosome 9 with the BCR segment on chromosome 22 [3]. The products of the BCR-ABL gene are various proteins that are dependent on the junction point in these two genes. The main of these products is the 2210 protein, which has abnormal tyrosine kinase activity, and this activity causes irregular cell proliferation and a decrease in the response of natural cell death to mutational stimuli [4,11]. Common symptoms of the disease include weight loss and anorexia, but 40% of patients are asymptomatic, and in this group of patients, only an abnormal blood cell count is effective in diagnosis [9]. In these patients, the white blood cell count increases to more than 25,000 per cubic millimeter, and all granulocytic differentiation classes are seen in their peripheral blood smear. Increased platelets are observed in 30 to 50% of these patients. Splenomegaly is a common abnormality in these patients during physical examinations and can be seen in half of the patients [3,4].

Corresponding author: Mohammad Mohammad Ali Mansouri
Email: Mansourii.dr@gmail.com

Bioinformatics, as an interdisciplinary science, analyzes biological and genetic data using computational tools and algorithms. In the diagnosis of cancers, this science helps researchers identify genetic and protein patterns associated with cancer. In leukemia in particular, bioinformatics can help identify specific mutations in the DNA of cancer cells, which can be useful for early diagnosis and the selection of targeted therapies. Also, using large databases and statistical analyses, it is possible to better understand disease trends and response to treatment [5].

Molecular docking is also recognized as a powerful tool in drug discovery and the design of new treatments. This method allows researchers to simulate the interactions between drug molecules and target proteins and predict how a drug might bind specifically to proteins associated with leukemia. Molecular docking can be used to identify new compounds that could serve as effective treatments for this type of cancer. This technique is especially crucial in the early stages of drug development, as it can help reduce the time and cost of research and development, ultimately leading to improved patient outcomes [1].

Nanoparticles, including gold, have attracted attention as a novel tool in cancer therapy due to their unique properties, including small size, high surface-to-volume ratio, and tunable optical properties. These nanoparticles can specifically bind to cancer cells and act as carriers for chemotherapeutic agents or therapeutic agents [7]. Using gold nanoparticles, drugs can be delivered to tumors in a targeted manner, resulting in fewer side effects to healthy tissues [8]. In addition, gold nanoparticles are also used in hyperthermia therapy, where they generate heat by absorbing infrared light and can destroy cancer cells. These properties have led to gold nanoparticles being investigated and investigated as a promising method for the control and treatment of cancers, especially in advanced stages of the disease [9,10].

Considering the special applications of the molecular docking technique and the special properties of gold nanoparticles, the aim of the present study is to investigate the effect of gold nanoparticles on the inhibition of BCR-ABL protein as a leukemia agent using the molecular docking method.

For this purpose, after designing and manufacturing the BCR-ABL protein and gold nanoparticles and modifying them molecularly, molecular docking will be performed to evaluate the possibility of ligand-protein molecular collision and the inhibitory power of gold nanoparticles on this protein. It is likely that gold nanoparticles can prevent the effects of leukemia to some extent by inhibiting this protein.

2. Experimental

2.1. Method

In this study, which was conducted using a descriptive-analytical method, molecular docking was used to simulate the interaction between gold nanoparticles and BCR-ABL protein. For this purpose, pymol version 2.6 software was used for molecular docking, and the PubChem and RCSB databases were used to extract molecular information.

2.2. Preparation of BCR-ABL Protein

First, the crystallographic structure of BCR-ABL protein with the identification code KF1601, resolution 2.2 Å, was downloaded in PDB format from http://www.rcsb.org. This enzyme consists of eight chains [A-H] and each chain has 72 amino acids (Fig. 1). Hydrogen atoms were added to the protein for correct ionization and tautomeric states of amino acid residues. Co-crystallized water molecules, forming one or more hydrogen bonds to either the protein or the ligand in the protein binding site, were kept in the calculation, whereas the remaining water molecules and inhibitors were extracted before the docking.

2.3. Preparation of Ligands

In this study, gold nanoparticles were modeled as a small cluster of several gold atoms to make their dimensions realistic compared to the K1F1 protein (Fig. 2). The nanoparticles were modeled assuming a spherical shape and an approximate size of 2.5 nm. To increase the accuracy of the simulation, seven gold atoms were chosen as the central core of the cluster to accurately simulate the effect of surface interactions with the active sites of the K1F1 protein.

The surface of the gold nanoparticles was free of any specific chemical modification to investigate the net effects of interactions with the active site of the protein. The nanoparticles were placed at random distances and different

orientations relative to the protein, and the docking simulation was repeated 50 times to determine the key interaction points.

2.4. Molecular docking

Then, using PyMOL software, the protein was displayed as a cartoon and the nanoparticles as spheres. To analyze the interactions, the distance between the nanoparticle atoms and the residues surrounding the protein (up to a radius of 5 Å) was examined, and hydrogen bonds and key interaction points were identified. Finally, 3D and 2D images of the interactions were saved for better visualization of the results. This approach offers a combination of accurate simulation and visual representation that is very useful for biophysical analysis and drug design [1].

Fig. 1. Three-dimensional structure of the BCR-ABL protein

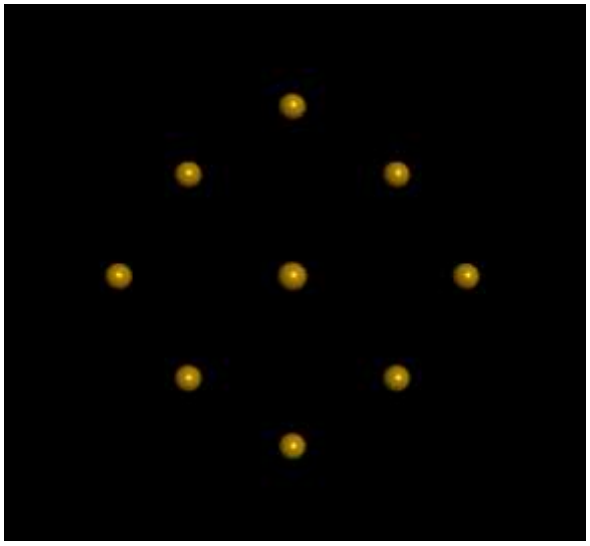

Fig. 2. Three-dimensional structure of the gold nanoparticles

3. Results and Discussion

The overall results of the docking of gold nanoparticles with the BCR-ABL protein, including the type of bond, amino acids involved in the pion, and the binding energy, are shown in Table 1. Also, Table 2 lists the types of van der Waals, hydrogen, and electrostatic interactions of gold nanoparticles with the aforementioned protein, and the distribution of interactions is shown in Fig. 3. The two-dimensional and three-dimensional structures of the docking of gold nanoparticles with the BCR-ABL protein are shown in Fig. 4 and Fig. 5.

In Fig. 4 gold nanoparticles are simulated in a realistic way. Molecular docking has been done in a way that shows a realistic simulation. Fig. 5. shows the interaction of gold nanoparticles (green) with amino acids. The molecular distance between the gold nanoparticles and the amino acids is also shown. The preferable binding of gold nanoparticles to BCR-ABL protein was through polar hydrophilic amino acids Arg 25 residue and through Tyr48, Ser 34, Also Ala16, Glu26, Arg23 form bond formation with gold nanoparticles. The measured distances between the surfaces of the gold nanoparticles and Arg residue obtained were 2.536 Å. However, 2.916 Å, 2.631 Å, 1.779 Å,2.563 Å, 2.920 Å and 1.972 Å is the bond length with respective amino acids of bound region as shown in Fig. 4. Therefore, these sites would be the probable binding sites of BCR-ABL protein with gold nanoparticles.

Table 1. Interaction of gold nanoparticles with the BCR-ABL subunit

Docking Run	Residue	Interaction	Energy [KCal/mol]
1	THR	Van der Waals	-7.37
2	ASP	Electrostatic	-5.8
3	THR	H-bond	-8.23
4	ARG	Electrostatic	-7.52
5	TYR	H-bond	-7.32
6	TYR	Van der Waals	-8.22
7	GLY	H-bond	-6.84
8	ARG	Electrostatic	-4.62
9	THR	Electrostatic	-7.66
10	HIS	H-bond	-6.94
11	LYS	Electrostatic	-7.16
12	TYR	H-bond	-5.22
13	TYR	H-bond	-4.98
14	GLU	Van der Waals	-6.7
15	THR	Electrostatic	-4.58
16	ALA	Van der Waals	-4.9
17	THR	Electrostatic	-6.62
18	HIS	H-bond	-8.81
19	GLU	Electrostatic	-5.65
20	THR	Van der Waals	-5.92
21	ASP	Electrostatic	-6.6
22	TYR	Van der Waals	-7.54
23	ARG	Van der Waals	-4.68
24	HIS	Van der Waals	-6.3
25	ARG	H-bond	-8.94
26	GLU	Van der Waals	-5.93
27	THR	Electrostatic	-5.71
28	TYR	H-bond	-4.22
29	TYR	H-bond	-8.53
30	THR	Van der Waals	-4.05

31	LYS	Electrostatic	-4.78
32	THR	Van der Waals	-8.54
33	ALA	Van der Waals	-6.21
34	SER	H-bond	-6.11
35	ARG	H-bond	-4.67
36	ARG	Electrostatic	-6.52
37	ALA	Electrostatic	-6.99
38	GLU	Van der Waals	-5.16
39	LYS	H-bond	-7.81
40	THR	Electrostatic	-5.28
41	SER	Van der Waals	-8.23
42	GLY	Van der Waals	-4.19
43	HIS	H-bond	-5.43
44	TYR	Electrostatic	-8.89
45	SER	H-bond	-8.39
46	HIS	Electrostatic	-4.47
47	HIS	Electrostatic	-7.86
48	TYR	H-bond	-6.09
49	TYR	H-bond	-7.05
50	THR	Electrostatic	-8.11

As can be seen from Table 1, the overall results of the docking of gold nanoparticles with the BCR-ABL protein, including the type of bond, amino acids involved in the pion, and the binding energy, confirmed the difference of binding energy. Also, Table 2 tabulated the types of van der Waals, hydrogen, and electrostatic interactions of gold nanoparticles with the aforementioned protein, and the distribution of interactions. Fig. 3 presents the Frequency of hydrogen, van der Waals and electrostatic bonds. As can be seen from Fig. 3, the electrostatic bond is more than hydrogen bond and hydrogen bonds are more than van der Waals band based on the results listed in Table. 1.

Table 2. Classification of types of interactions of gold nanoparticles with the BCR-ABL subunit

Interaction	**Residue**
Electrostatic	THR[1]- ASP[2]- ARG[4]- ARG[8]- THR[9]- LYS[11]- THR [15]- THR[15]-GLU[19]- ASP[21]- THR[27]- LYS[31]- ARG[36]- ALA[37]- THR[40]- TYR[44]- HIS[46]- HIS[47]- THR[50[
H-bond	TYR[3]- TYR[5]-GLY[7]-HIS[10]-TYR[12]- TYR[13]-HIS[18]-ARG[25]-TYR[28]-TYR[29]- SER[34] ARG[35]-LYS[39]-HIS[43]-SER[45]- TYR[48]-TYR[49[
Van der Waals	THR[1]-TYR[6]-GLU[14]-ALA[16]-THR[22]- ARG[23]-HIS[24]-GLU[26]-THR[30]-THR[32]- ALA[33]-GLU[38]-SER[41]-GLY[42[

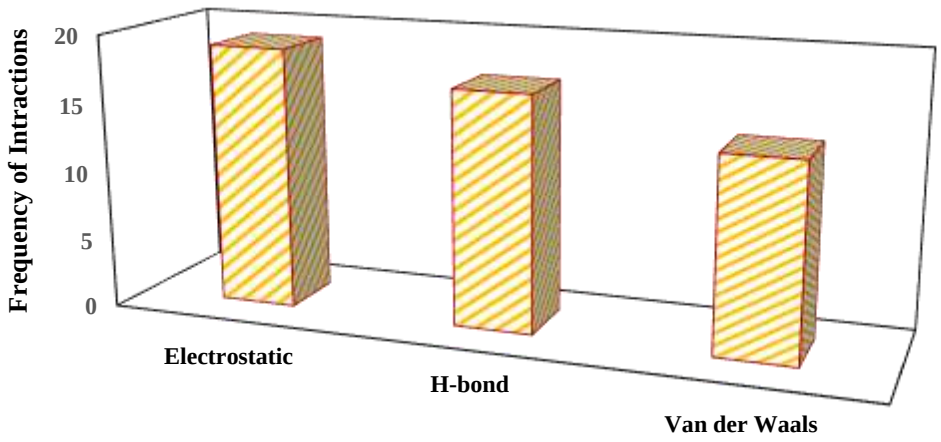

Fig. 3. Frequency of hydrogen, van der Waals and electrostatic bonds

The two-dimensional and three-dimensional structures of the docking of gold nanoparticles with the BCR-ABL protein are shown in Fig. 4 and Fig. 5. As can be seen from Fig. 4 the gold nanoparticles are simulated in a realistic way. Molecular docking has been done in a way that shows a realistic simulation. Fig. 5. shows the interaction of gold nanoparticles (green) with amino acids. The molecular distance between the gold nanoparticles and the amino acids is also shown. The preferable binding of gold nanoparticles to BCR-ABL protein was through polar hydrophilic amino acids Arg 25 residue and through Tyr48, Ser 34, Also Ala16, Glu26, Arg23 form bond formation with gold nanoparticles. The measured distances between the surfaces of the gold nanoparticles and Arg residue obtained were 2.536 Å. However, 2.916 Å, 2.631 Å, 1.779 Å,2.563 Å, 2.920 Å and 1.972 Å is the bond length with respective amino acids of bound region as shown in Fig. 4. Therefore, these sites would be the probable binding sites of BCR-ABL protein with gold nanoparticles.

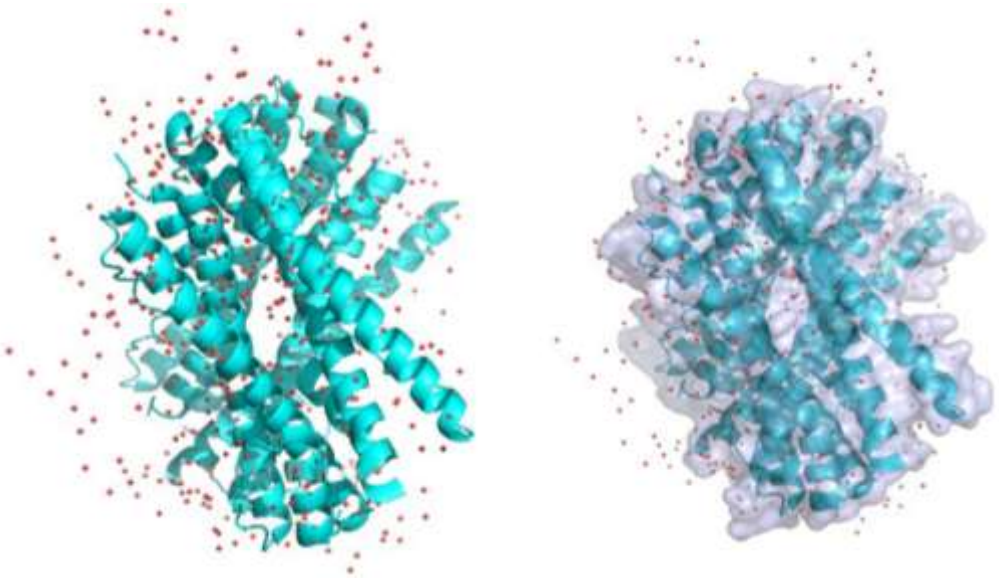

Fig. 4. Network interaction of gold nanoparticles with BCR-ABL protein [3D view].

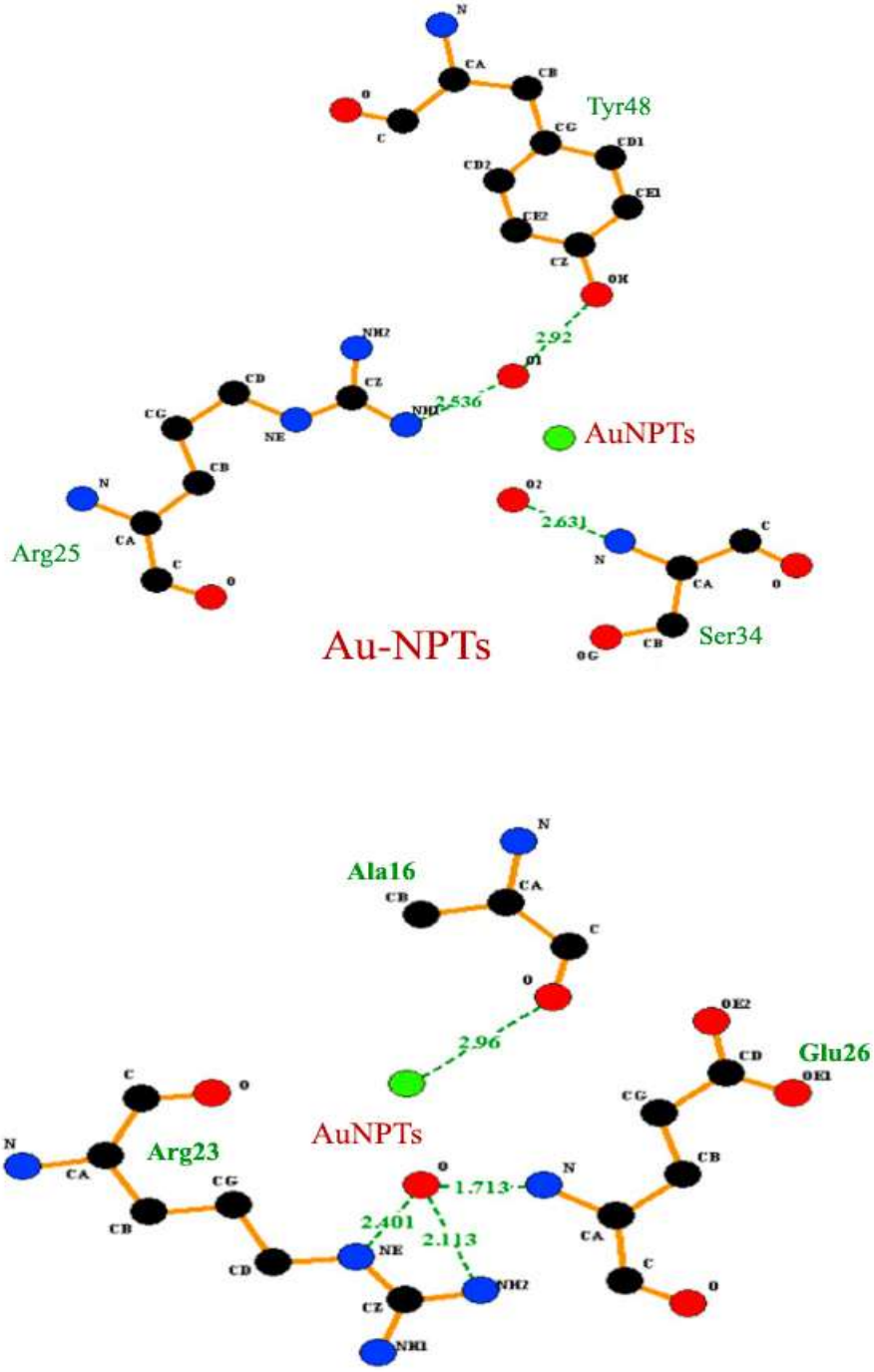

Fig. 5. Examples of network interaction of gold nanoparticles with BCR-ABL protein [2D view].

4. Conclusion

The molecular docking study of gold nanoparticles on BCR-ABL protein in leukemia demonstrates the high potential of these nanoparticles in inhibiting the activity of this protein. The interactions established through hydrogen bonds, electrostatic and van der Waals forces with a suitable number of amino acids of this protein clearly indicate that gold nanoparticles can act as an effective agent in reducing BCR-ABL activity. So far, no specific study has been

conducted on the interaction of gold nanoparticles on BCR-ABL protein. Pang et al. reported that gold nanoparticles cause dose-dependent gaps in the endothelial walls of blood vessels to accelerate the formation of CTCs and can be effective in the treatment of leukemia. These findings not only demonstrate the importance of gold nanoparticles as a novel therapeutic tool in the treatment of leukemia, but also contribute to a deeper understanding of the molecular mechanisms involved in this type of therapy. In addition, the results obtained from this study can serve as a basis for further research in the field of developing nanoparticle-based therapies. Given the potential of gold nanoparticles in inhibiting the BCR-ABL protein, it is suggested that this method be supplemented and investigated more precisely using laboratory techniques. In vitro and in vivo experiments can help confirm the efficacy and safety of these nanoparticles in real conditions and pave the way for the development of new and effective drugs for the treatment of leukemia.

Acknowledgments

I would like to thank the aforementioned colleagues who helped me prepare and review this research.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author information

*Corresponding Author: Mohammad Mohammad Ali Mansouri
Email: Mansourii.dr@gmail.com

References

[1] P. C. Agu, C. A. Afiukwa, O. U. Orji, et al. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. Sci. reports. 13(1) (2023) 13398. https://doi.org/10.1038/s41598-023-40160-2

[2] G.P. Amarante-Mendes, A. Rana, T. S. Datoguia, N. Hamerschlak, G. Brumatti. BCR-ABL1 Tyrosine Kinase Complex Signaling Transduction: Challenges to Overcome Resistance in Chronic Myeloid Leukemia. Pharmaceutics, 14(1) (2022) 215. https://doi.org/10.3390/pharmaceutics14010215

[3] F. Carofiglio, D. Trisciuzzi, N. Gambacorta, et al. Bcr-Abl Allosteric Inhibitors: Where We Are and Where We Are Going to. Molecules, 25(18) (2020) 4210. https://doi.org/10.3390/molecules25184210

[4] C. Cumbo, L. Anelli, G. Specchia, F. Albano. Monitoring of Minimal Residual Disease [MRD] in Chronic Myeloid Leukemia: Recent Advances. Cancer man., 12(2020) 3175–3189. https://doi.org/10.2147/CMAR.S232752

[5] M. El-Tanani, H. Nsairat, I. I-Matalka, et al. The impact of the BCR-ABL oncogene in the pathology and treatment of chronic myeloid leukemia. Pathology, res & practice, 254(2024) 155161. https://doi.org/10.1016/j.prp.2024.155161

[6] J. M. Goldman, J. V. Melo. Melo mechanisms of disease, chronic myeloid leukemia advances in biology and new approaches to treatment. MMS. 349(2003) 1451-61. https://doi.org/10.1056/NEJMra020777

[7] S. Jain, D. G. Hirst, J. M. O'Sullivan. Gold nanoparticles as novel agents for cancer therapy. BJR, 85(2012) 101–113. https://doi.org/10.1259/bjr/59448833

[8] W. Pang, S. Ding, L. Lin. Noninvasive and real-time monitoring of Au nanoparticle promoted cancer metastasis using in vivo flow cytometry. BOEx, 12(4) (2021) 1846–1857. https://doi.org/10.1364/BOE.420123

[9] A. Quintás-Cardama, J. Cortes. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood, 113(8) (2009) 1619–1630. https://doi.org/10.1182/blood-2008-03-144790

[10] J. Chen, D. J. DeAngelo, J. L. Kutok. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. Bio Sci., 101 (2004) 14479-14484. https://doi.org/10.1073/pnas.040443810

[11] Zhu, H. Q. Gao, F. H. Regulatory Molecules and Corresponding Processes of BCR-ABL Protein Degradation. J. Cancer, 10(2019) 2488–2500. https://doi.org/10.7150/jca.29528