Summary:

Chronic myeloid leukemia is a type of blood cancer that occurs due to a mutation in the white blood cell precursors in the bone marrow of affected people. This mutation is a translocation and will take place between chromosomes 9 and 22. Despite notable improvements in the chemical treatment of cancers, resistance to many drugs has recently become a complicated issue. Various factors, including activation or inactivation of cellular signaling pathways, can contribute to drug resistance. The hippo signaling pathway is one of the pathways that play a key role in developing drug resistance. This signaling pathway controls cell growth and differentiation and the size of various organs in the body. In addition, upregulation or downregulation of the expression of genes encoding key components of the hippo signaling pathway is significant in cell abnormal growth and drug resistance. Chemicals, other signaling pathways, proteins, and microRNAs (miRs) are some of the factors that can affect the upregulation and downregulation of hippo signaling pathway components. MiRs, as 19- to 25-nucleotide non-coding sequences, can play a significant role in regulating the expression of many genes within the cell. These miRs can decrease or increase the translation of proteins at different levels of the gene translation process via interacting with messenger RNAs. In various cancers, the overall intracellular miRs decrease, but sometimes, some intracellular miRs are overexpressed following the development of cancer. This study analyzed the expression of *miR-135a-5p, miR-125b-2-3p, miR-182-5p, miR-103a-3p, miR-590-3p,* and *miR-29b-3p* via USLP method. Also, the correlation of their expression changes with survival, growth, proliferation, and ROS level in K-562 cells treated with $IC_{50}$ of imatinib in two treatments of 12 and 48 hours was evaluated. In the following, the level of expression of the main components of the hippo signaling pathway, including *SAV1, STK4, STK3, MOB1A, MOB1B, LATS1, LATS2*, and *YAP*, and its relevance with the expression level of the mentioned microRNAs was assessed. *MiR-135a-5p, miR-125b-2-3p, miR-182-5p,* and *miR-103a-3p* were up-regulated both after 12 hours and after 48 hours of treatment compared to the control; But this increase was more obvious after 48 hours. This suggests that these microRNAs, in line with inhibiting the growth and proliferation of most cells in 48 hours, probably have a tumor suppressor role in CML. The expression level of all microRNAs, except *miR-29b-3p*, increased at 48 hours compared to 12 hours. The expression of *miR-590-3p* decreased after 12 hours and increased after 48 hours of treatment compared to the control. The expression of *miR-29b-3p* also increased in both 12- and 48-hour treatments compared to the control, but this increase was more significant in the 12-hour treatment. The expression level of the mRNA of all investigated components of the hippo signaling pathway increased significantly and significantly after 12 hours of treatment with imatinib compared to the control. However, this increase in expression in the 48-hour treatment was not significant compared to the control. The expression of *LATS2* was significantly increased at 12 hours compared to the control. On the other hand, *STK4* (*MST1*) and *YAP* genes were down-regulated in the 48-hour treatment compared to the control; But this decrease in expression was not significant. The expression level of all components of the hippo signaling pathway after 48 hours of treatment, compared to the 12-hour treatment, significantly decreased. In conclusion, our results demonstrated that imatinib could possibly affect the expression of components of the hippo signaling pathway through microRNAs.

Key words: CML, Non-coding RNAs, Hippo signaling pathway, Targeted therapy, Leukemia.