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Inhibition of TNF-Alpha using Plant-Derived Small Molecules for Treatment of Inflammation-Mediated Diseases

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Abstract

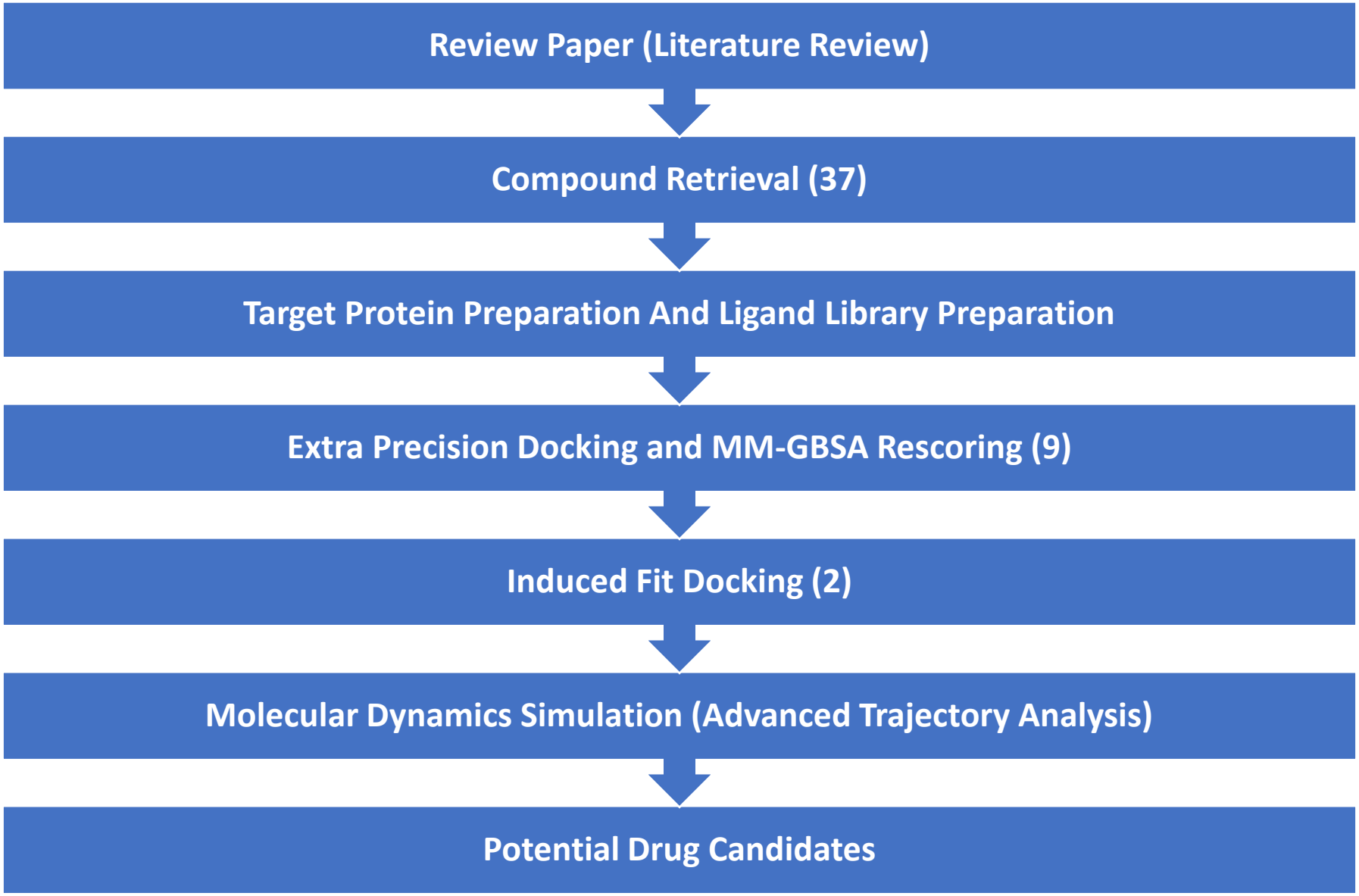
Inhibition of TNF-α has become a feasible target for alleviating inflammation-mediated diseases. Currently, techniques developed, such as anti-TNF antibody therapies, prove not to be nearly as beneficial enough to effectively treat inflammation-mediated syndromes because of the increased risk for severe infections and malignancies. Our study has undertaken the attempt of identifying small molecules to inhibit TNF-α. This study manually selected 37 plant-derived compounds based on IC50 value from various literature, which showed inhibitory activity against TNF-α. By employing an *in silico* pipe-line, we have aimed to explore the binding modes, to discover the most possible mechanism of inhibition, as well as, for a deeper understanding of structural changes, which is necessary for rationalization of the targeted inhibition by our proposed bioactive compounds. Therefore, this study has identified two potential compounds through advanced induced fit docking and simulation study. The stability of protein-ligand complex and structural changes was studied by performing 100ns molecular dynamics simulation with its binding energy estimated through MM-PBSA analysis.

Keywords: Inhibition of TNF-α; Plant-Derived Small Molecules; Inflammation-Mediated Diseases; Exploration of the Inhibitory Sites; Promising Potential Inhibitors.

Introduction

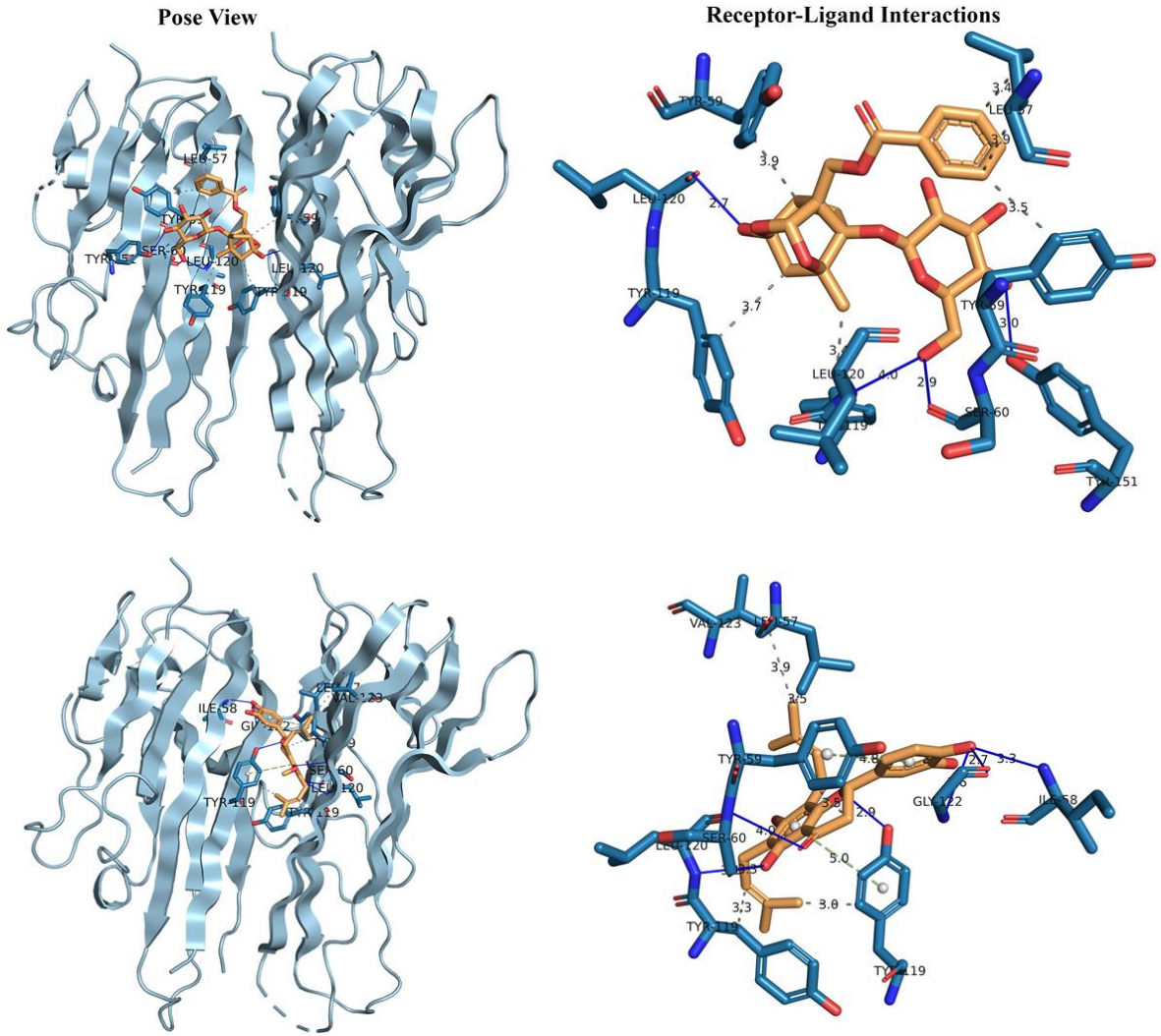
- Tumor necrosis factor-alpha (TNF-α), is a pleiotropic inflammatory cytokine trimeric protein, encoded within the major histocompatibility complex. TNF-α is believed to play a significant role in the response of the innate immune system, inflammation associated carcinogenesis and different pathophysiological function.
- TNF plays a critical role in a diverse range of inflammatory, infectious and malignant diseases. Inhibition of TNF was proved to be effective against; Rheumatoid Arthritis, Ankylosing Spondylitis, Inflammatory Bowel Disease, Psoriasis, Respiratory Diseases, Cardiovascular Diseases, Renal Diseases, Diseases of the Central Nervous System and a number of other inflammatory diseases.
- As a pro-inflammatory cytokine, the expression of TNF could be high, as seen in inflammation and most aspects of carcinogenesis. It has already been suggested that serum TNF levels could be an indicator for understanding chemotherapeutics' response and prognosis.
- Since the 1980s, several attempts have been taken to develop potential inhibitors against TNF alpha, and protein-based drugs such as; etanercept, infliximab, adalimumab have been approved by the FDA. However, these first-generation inhibitors have several adverse effects, such as; cognitive heart failure, activation of latent tuberculosis, increased probability of cancer.
- Following that, studies have suggested that the development of small molecules against the receptors, are more applicable and ideal for long term use and could potentially be used in combination with other anti-inflammatory therapies.

Methodology



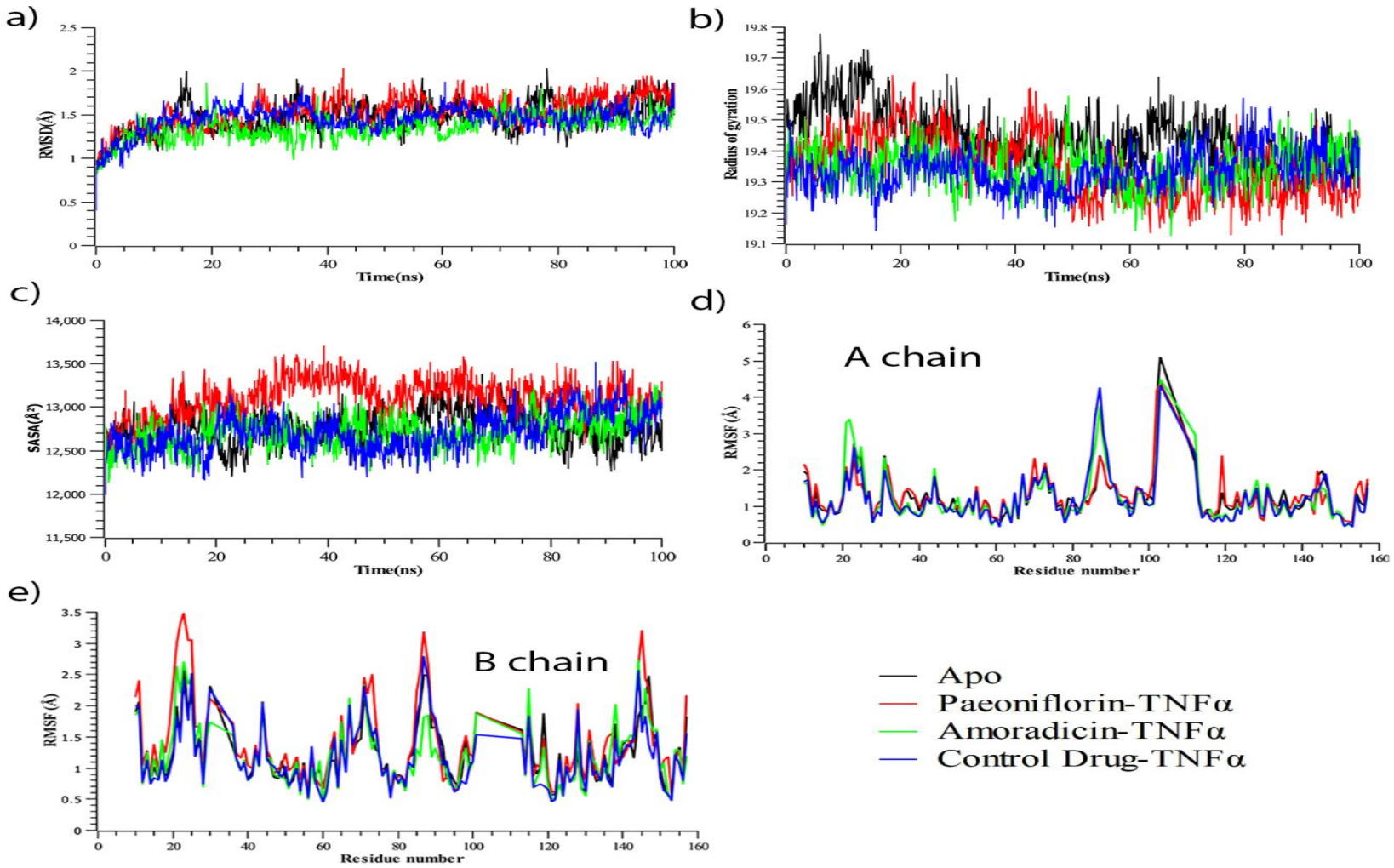
Result & Discussion

- **Figure 1: Interaction of Paeoniflorin and Amoradicin within active site residue of TNF-alpha:**



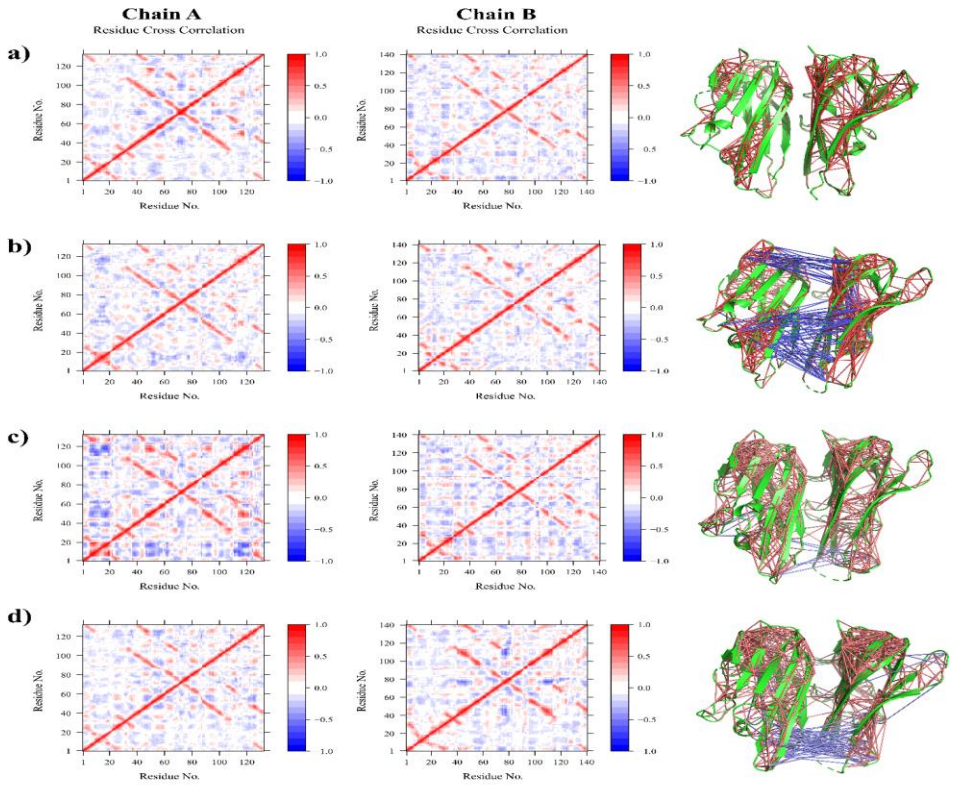
Result & Discussion

❑ Figure 2: Molecular Dynamics simulation

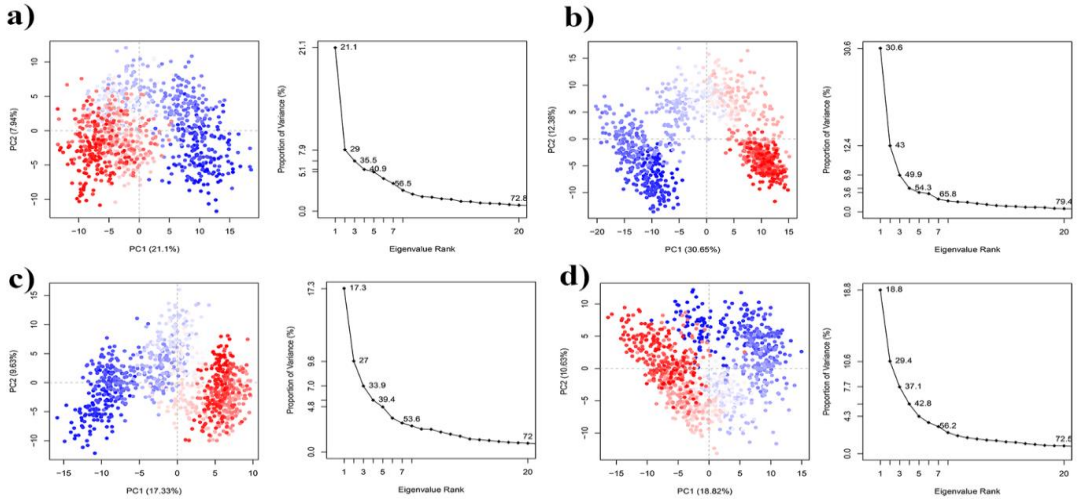


Result & Discussion

- **Fig 3: Residue cross correlation maps of a) Apo, b) Paeoniflorin-TNFα complex c) Amoradicin-TNFα complex, and d) Control drug- TNFα complex.**



- **Figure 4: Principle component analysis**



- **Residue flexibility and conformational analysis**

Figure 5:

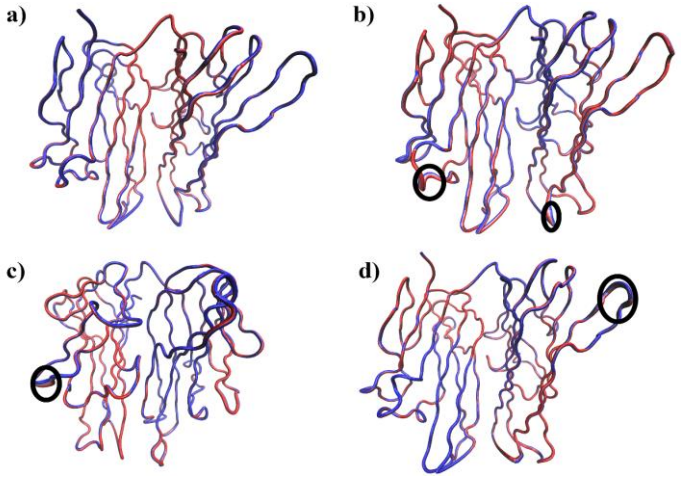
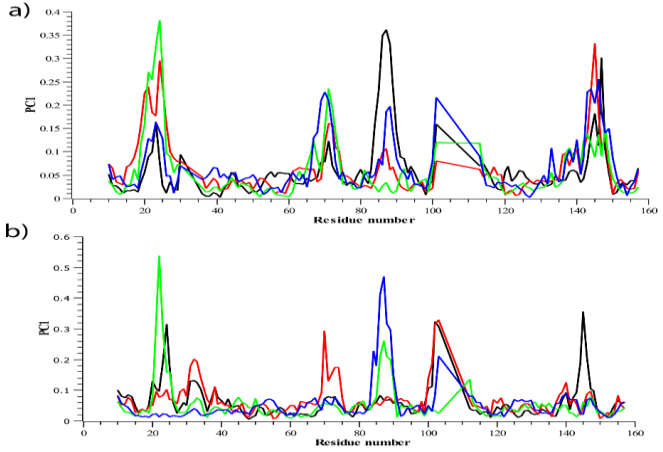
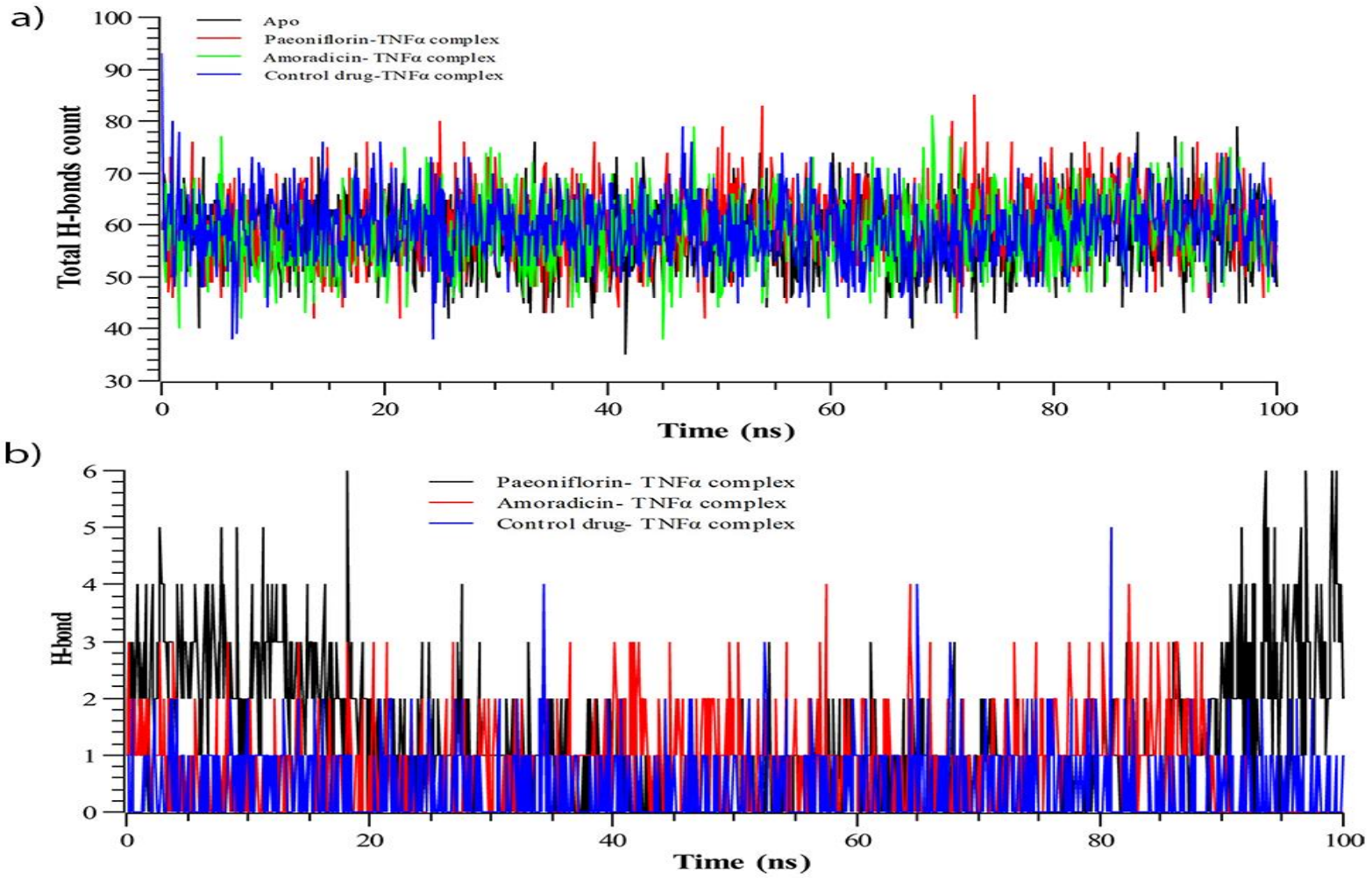


Figure 6:



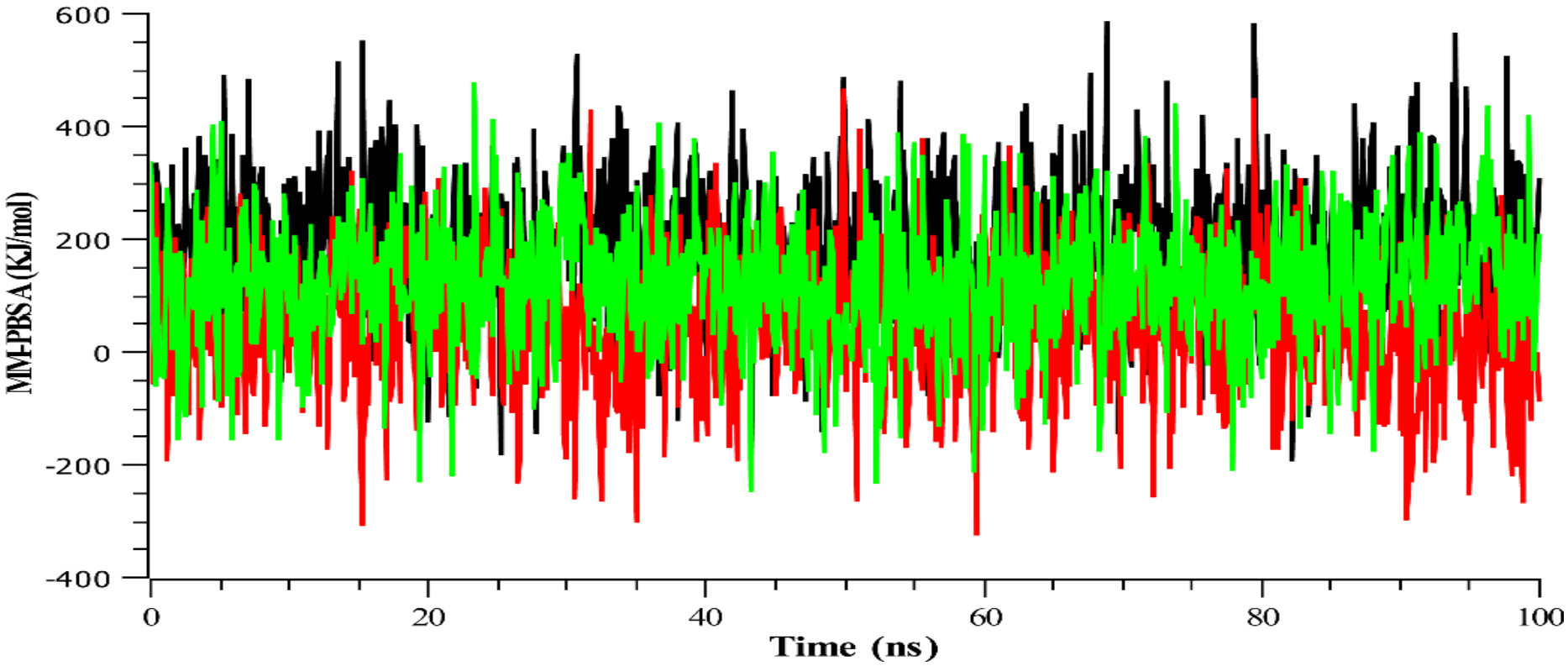
Result & Discussion

❑ Figure 7: Hydrogen bond analysis



Result & Discussion

❑ **Figure 8: Binding free energy of all protein-ligand complexes**



Conclusion

This study highly recommends two compounds such as paeoniflorin and amoradicin as potential inhibitors of TNF-α. The co-crystalized ligand was used as a control to compare binding modes, inhibiting mechanism, and dynamic behavior of newly proposed inhibitors. So, our findings could be useful to the next fellow researches in case of any modifications prior to the lead optimization and future drug development process to inhibit TNF- α.

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