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Title of the Presentation

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

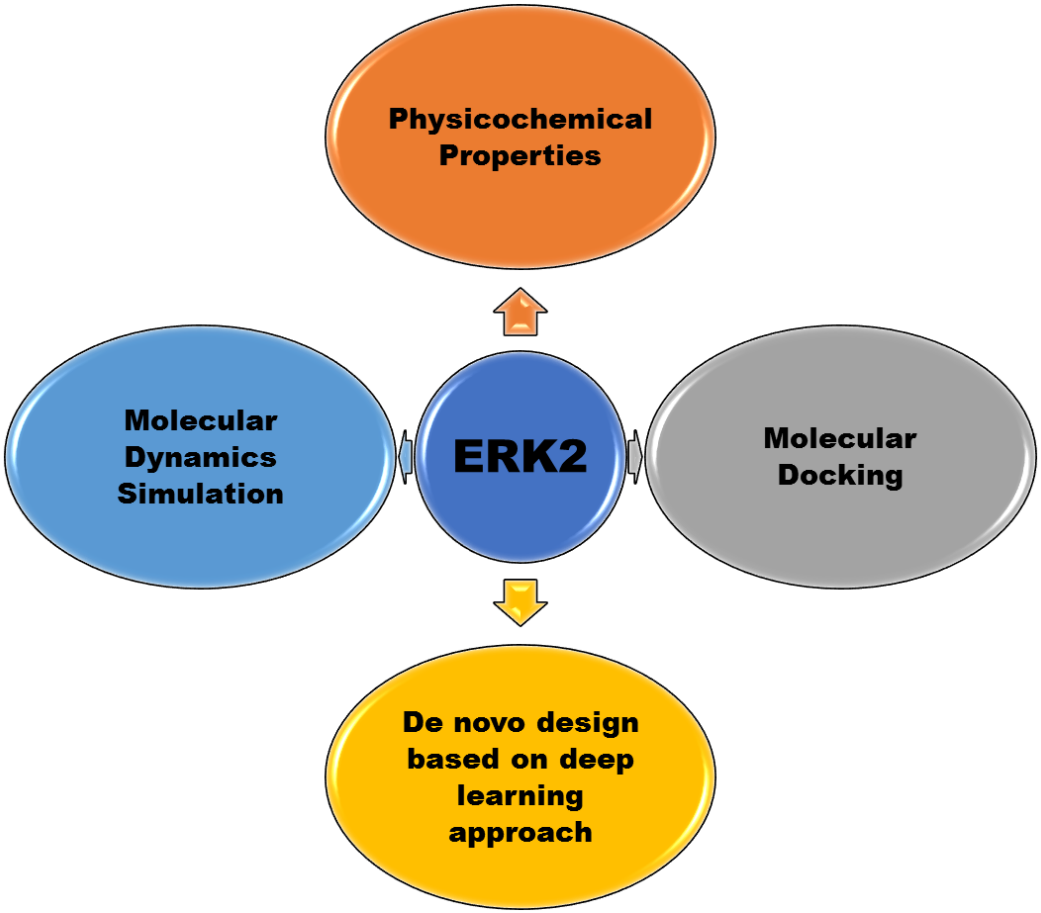
pharmaceuticals MDPI

Eslam Mohamed [1,*], Ahmad Al-Khdhairawi [2], and Sara Safwat Muhammed [2]

[1] Department of Chemistry, Faculty of Science, Minia University, Minia, 61511, Egypt
[2] Department of Biological Science and Biotechnology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor, Malaysia
[3] Faculty of Pharmacy for girls-AlAzhar University, Banha, 13511, Egypt

* Corresponding author: eslamahmedragabmohamed@gmail.com

Introducing novel ERK2 Inhibitors via *de novo* drug design supported by Molecular Docking, Physicochemical properties, and Molecular Dynamics Study



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Abstract:
Extracellular signal-regulated kinase 1/2 (ERK1/2) is a serine/threonine protein kinase in eukaryotic cells and belongs to the mitogen-activated protein kinase (MAPK) family. ERK1/2 is essential for signaling from surface receptors to the nucleus. Activated ERK1/2 phosphorylates substrates in the nucleus or cytoplasm, causing certain proteins to be expressed or activated, regulating cell proliferation, differentiation, death, and other functions. ERK1/2 is abundantly expressed in several forms of ischemia-reperfusion injury (IRI). Caffeic acid (3,4-dihydroxy cinnamic acid), as previously reported, interacted directly with ERK1/2 and reduced its actions *in vitro*. Moreover, it is reported to have a variety of pharmacologic effects, including anti-inflammatory, immunomodulatory, antioxidant, and anticancer effects. In the present study, we employ a deep learning protocol to generate novel and effective anti-ERK1/2 drugs by modifying the chemical structure of caffeic acid, aiming to improve its inhibition performance. Instead of conventional experimental methods, computer-aided drug design (CADD) can be an effective, rapid, and cost-efficient method to design novel drugs. In the current study, a molecular docking as well as a molecular dynamics study will be executed to explore the effectiveness of the generated drugs.

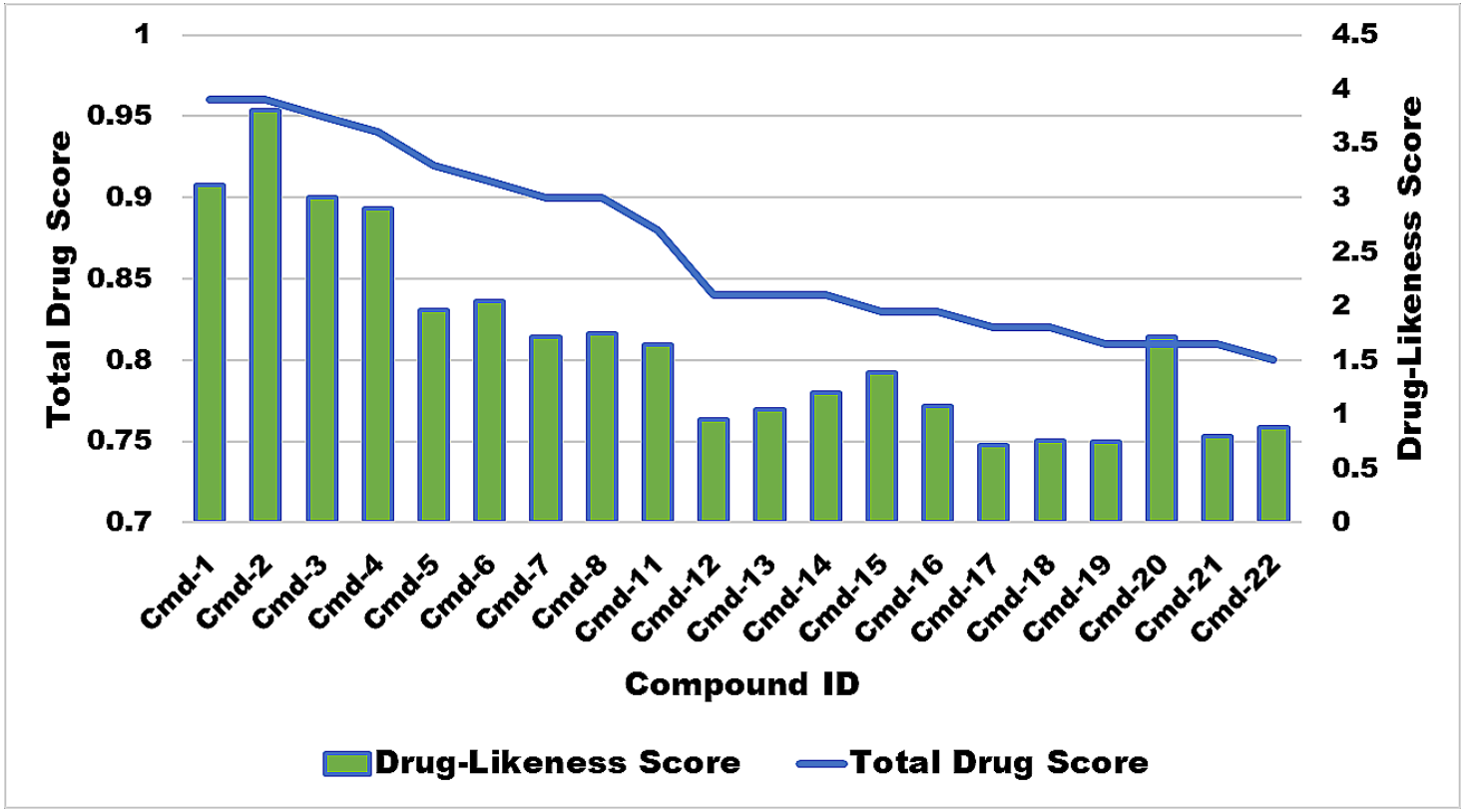
Keywords: CADD, Caffeic acid, ERK1/2, Molecular docking, Molecular dynamics.

Introduction

Extracellular signal-regulated kinases (ERK1 and ERK2) are members of the mitogen-activated family, also known as mitogen-activated protein kinases (MAPKs). The amino acid sequences of ERK1 and ERK2 are 85% identical. ERK1 and ERK2 are critical targets in various malignancies, including breast, lung, prostate, and ovarian cancer. Coffee contains a well-known phenolic phytochemical compound known as caffeic acid (CA) or 3,4-dihydroxycinnamic acid, which has a wide range of anticancer properties. Deep learning (DL), a subset of machine learning (ML), has recently been used extensively in the identification of novel compounds as a starting point for the production of bioactive drugs. In the ongoing study, a deep learning algorithm for *de novo* design of drug-like compounds was employed as an effective tool for finding novel ERK2 inhibitors based on the CA structure. To save time, effort and money, computer-aided drug design (CADD) can be used as an effective way for drug discovery. For this purpose, various *in silico* approaches such as molecular docking, computer-aided drug score evaluation, and molecular dynamics simulations (MD) have been applied to investigate the effects of the compounds under inspection.

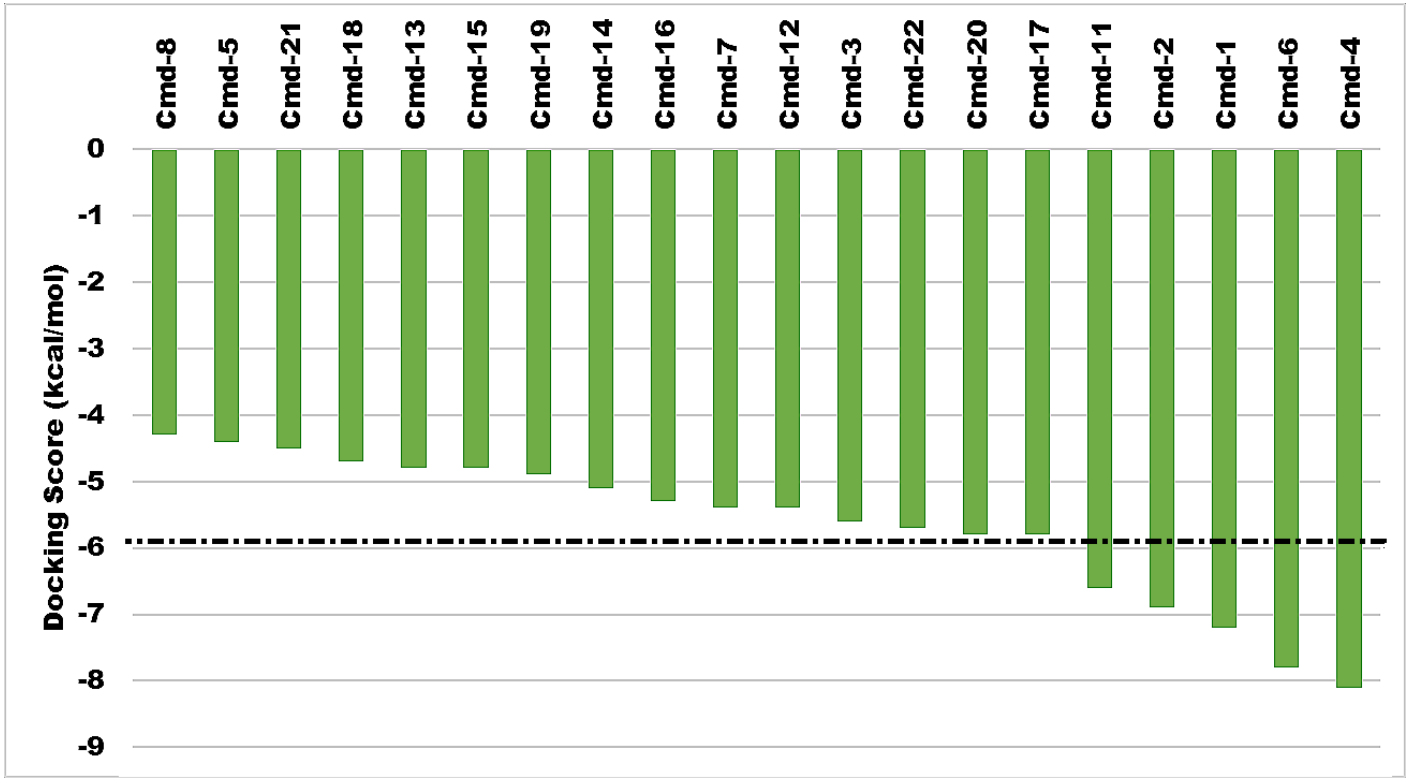
Results and discussion

As a first stage, the physicochemical properties of the generated compounds were evaluated and compared to the parent compound. Twenty-two compounds out of a total of one hundred showed favorable behavior in terms of drug-likeness and drug score.



Results and discussion

Molecular docking was employed as a useful in silico approach in studying the activity of those towards ERK2. According to the results of molecular docking studies, five compounds achieved substantial docking scores ranging from -6.6 to -8.1 kcal/mol, indicating their relative stability when compared to CA (-5.9 kcal/mol).



Conclusions

The current study aimed to develop novel, effective inhibitors of ERK2. Deep learning was used as an efficient way in the drug design process instead of traditional methods such as drug repurposing or database filtration. Based on the chemical structure of caffeic acid, one hundred compounds were generated and inspected. Drug-likeness and drug score calculations revealed that twenty-two compounds have promising features. The best-reached compounds were subjected to molecular docking calculations to map the interacting ERK2 residues and measure the affinity of the formed protein-ligand complex. Molecular dynamics over 200 ns will be applied to asses the stability of each compound inside the ERK2 active site. The new findings show that deep learning can be used to produce effective and unique molecules based on a parent molecule.

Acknowledgments

Not applicable.