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In silico Computational Study of Cinnamon (*Cinnamomum verum*) Bioactive Compounds as Cancer-Immunotherapy Drug Candidate Targeting RAS-JAK-ERK Signaling Pathway to Inhibit the Programmed Death Protein Ligand 1 (PD-L1) Expression

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Abstract. Immunotherapy is the current and an alternative therapy option for cancer. Targeting PD-L1 expression provides one approach for limiting cancer progression. Cinnamon is a plant with medicinal properties that is also commonly used as a spice. Previous study indicates that cinnamon has multiple therapeutic effects because it is utilized to treat a variety of diseases. The purpose of this research is to examine the potential of bioactive compounds derived from cinnamon as potential cancer immunotherapy agents through the inhibition of PD-L1 expression. In the present investigation, *in silico* approaches were used, which included molecular docking and predicting the biological activity of cinnamon bioactive compounds. According to the findings, the active compound of cinnamon was effective and had the potential to inhibit the JAK protein, but not RAS or ERK. Furthermore, according to the biological activity predictions, cinnamon bioactive compounds contribute as cancer fighting agents by having high Pa values for several parameters such as antineoplastic, apoptosis agonist, BRAF expression inhibitor, JAK2 expression inhibitor, and Myc inhibitor also low Pa values for M-CSF agonists. Finally, more detailed research on cinnamon bioactive compounds, particularly caryophyllene, is required.
Keywords: Cancer-immunotherapy; ERK; JAK; PD-L1; RAS.

Resumen. La inmunoterapia es la opción terapéutica alternativa actual para el cáncer. Usar como blanco la expresión de PD-L1 ofrece un enfoque para limitar la progresión del cáncer. La canela es una planta con propiedades medicinales que también se usa comúnmente como especia. Estudios previos indican que la canela tiene múltiples efectos terapéuticos, ya que se utiliza para tratar diversas enfermedades. El propósito de esta investigación es examinar el potencial de los compuestos bioactivos derivados de la canela como posibles agentes de inmunoterapia contra el cáncer mediante la inhibición de la expresión de PD-L1. En la presente investigación, se utilizaron enfoques *in silico*, que incluyeron el acoplamiento molecular y la predicción de la actividad biológica de los compuestos bioactivos de la canela. Según los hallazgos, el compuesto activo de la

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canela fue eficaz y tenía el potencial de inhibir la proteína JAK, pero no RAS ni ERK. Además, según las predicciones de la actividad biológica, los compuestos bioactivos de la canela contribuyen como agentes anticancerígenos al presentar altos valores de Pa para diversos parámetros, como antineoplásico, agonista de la apoptosis, inhibidor de la expresión de BRAF, inhibidor de la expresión de JAK2 e inhibidor de Myc, así como bajos valores de Pa para agonistas del M-CSF. Finalmente, se requiere una investigación más detallada sobre los compuestos bioactivos de la canela, en particular el cariofileno.
Palabras clave: Inmunoterapia contra el cáncer; ERK; JAK; PD-L1; RAS.

Introduction

Nearly 2 million new cancer diagnoses and approximately six hundred thousand cancer deaths are expected in the United States in 2023 [1]. According to the recent study, lung cancer will still be the primary cause of cancer-related mortality in 2040, accounting for 63,000 deaths, while breast cancer will account for 364,000 cases of cancer overall [2]. Ironically about 35 % of global cancer-related mortality can be attributed to lifestyle-related risk factors that are conceivably modifiable. These risks include smoking, alcohol intake, infections, parasites, exposure to UV radiation, and nutritional factors [3]. For instance, a study showed the excessive caloric consumption and insufficient physical activity are linked to elevated adipose tissue accumulation, which ultimately results in overweight, obesity, and cancer [4].

The classifications of cancer treatment are divided into conventional and advanced categories. Presently, established conventional treatment modalities, including surgery, chemotherapy, and radiotherapy, continue to be employed. However, noteworthy progressions in recent years have been observed in the form of targeted therapies, nanoparticles, hormonal therapy and stem cell therapy. Currently, oncology techniques have their emphasis on the creation of safe and efficient cancer treatments [5,6].

Immune checkpoint inhibitors are examples of immunotherapy, a type of cancer treatment that uses immune system components to combat tumor cells [7]. In various cancer cases, immunotherapy—either by itself or in conjunction with conventional approaches such radiation and chemotherapy—has shown favorable outcomes when utilized alongside standard care. PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors are three distinct classes of immune checkpoint inhibitors that have been used to treat different kinds of cancer. However, only a small percentage of individuals recover from this treatment. A number of variables determine immunotherapy outcomes, including tumor mutational burden, PD-L1 expression, hypoxia, extracellular matrix, and molecular and cellular characterization within the tumor microenvironment [7,8]

In order to decrease T cell activation and the immunological response of T cells specific to antigens, tumors overstimulate the PD-1/L1 signaling pathway. Apart from PD-L1 expression, cancer cells also trigger intrinsic cellular signals that improve cancer cell survival, control stress reactions, and strengthen tumor resistance to pro-apoptotic agents like interferons [7]. A study showed the stimulation of interferon could increasing the expression of PD-L1 through JAK/STAT signaling pathway [9]. Another study in cholangiocarcinoma cell lines showed that PD-L1 expression is modulated via ERK signaling [10]. Thus, by blocking the signaling pathways that involved in PD-L1 expression might contribute in the anti-tumor surveillance system. Recently, some immune checkpoint inhibitors have been proposed for targeting PD-1/PD-L1, however, unfortunately, some additional adverse events also appears which need serious attention to solve [11,12].

Recently, medicinal plants and their bioactive components have gained popularity as immunomodulation and complementary cancer treatments [13-18]. Numerous clinical investigations have found that medicinal plants improve survival, immunological regulation, and quality of life [19,20]. On a large scale, cinnamon can be found in tropical regions. Cinnamon is widely utilized on a daily basis throughout the globe and is regarded as one of the most essential spices. Importantly, cinnamon has antioxidant, anti-inflammatory, antidiabetic, antibacterial, anti-obesity, and anticancer properties [21,22]. Interestingly, a study showed that cinnamon extract inhibit the melanoma cell lines progression by reducing some factors related to the angiogenesis. Moreover, the study also demonstrated that cinnamon extract increase the activity of CD8+ T cells which were known for its anti-tumor activity [23]. In light of the aforementioned, the intent of this study

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is to determine the potential of bioactive compounds found in cinnamon as a cancer immunotherapy drugs candidate by blocking PD-L1 expression.

Experimental

Data retrieval and preparation

Bioactive compounds that widely found in cinnamon were occupied in this study [24]. The chemical structure of bioactive compounds was retrieved from The PubChem database (https://pubchem.ncbi.nlm.nih.gov/). About nine bioactive compounds (Fig. 1) including camphor (CID. 2537); caryophyllene (CID. 5281515); caryophyllene oxide (CID. 1742210); cinnamaldehyde (CID. 637511); eugenol (CID. 3314); trans-alpha-bergamotene (CID. 6429302); trans-cinnamyl acetate (CID. 5282110); α-bergamotene (CID. 86608); and α-copaene (CID. 442355) were retrieved together with three control drugs including RAS inhibitor/ Tipifarnib (CID. 159324); JAK inhibitor/ Ruxolitinib (CID. 25126798); and ERK inhibitor/ GDC-0994 (CID. 154702204). In order to provide target proteins, homology modelling approach was applied. The sequences of target protein were retrieved from UniProt (https://www.uniprot.org/) and the 3D structure of target proteins was built through SWISS-MODEL (https://swissmodel.expasy.org/) as our previous study [25-27]. The detailed UniProt ID and protein template of each target proteins are RAS (UniProt ID. P01112/ template 4q21.1.A); JAK (UniProt ID. P23458/ template 7t6f.1.A); and ERK (UniProt ID. P28482/ template 4qtb.1.A).

Molecular docking and data visualization

Molecular docking was performed by using PyRx (https://pyrx.sourceforge.io/) software [28,29]. Prior to docking process, the whole structure of each target proteins was aimed by bioactive compounds and control drug. The center coordinates for each target protein (Å) are RAS (X= 57.1120; Y= 71.3046; Z= 40.5094); JAK (X= 178.123; Y= 198.282; Z= 171.913); and ERK (X= 33.2178; Y= 46.6949; Z= 56.9310). Molecular coverage area (Å) for each target proteins are RAS (X= 39.8465; Y= 43.3056; Z= 42.5991); JAK (X= 85.5510; Y= 72.0893; Z= 148.8165); and ERK (X= 60.5657; Y= 47.6961; Z= 69.0495). After molecular docking was performed, the data visualization then was conducted by using Biovia Discovery Studio (https://discover.3ds.com/) software. Several parameters including protein – ligand interaction, amino acids residues, H-bond, and hydrophobicity were visualized and analyzed [30,31].

Biological activity prediction

Biological activity prediction was performed on bioactive compounds derived from cinnamon through the Way2Drug (https://www.way2drug.com/PassOnline/index.php) webserver. The purpose of this prediction was to determine the effectiveness as well as the potential of the active compound derived from cinnamon with regarding a variety of distinct biological activities. Some parameters were evaluated including antineoplastic, apoptosis agonist, BRAF expression inhibitor, JAK2 expression inhibitor, Myc inhibitor, M-CSF agonist.

Results and discussion

It has been widely known that, the expressed PD-L1 on cancer cells interacts to the PD-1 on immune cells promotes cancer progression and cancer immune escape. Therefore, the recent immunotherapy strategy is to block the PD-1/ PD-L1 interaction which in turn could optimize the T cells function, reducing the regulatory T cells activity, and other immune mechanisms in eliminating cancer cells [32,33]. Another strategy which might work is to limiting the PD-L1 expression on the cancer cells by targeting RAS-JAK-ERK signaling pathways [34,35]. In this present study, we evaluated the therapeutic properties of cinnamon bioactive compounds through computational assessment and biological activity prediction.

According to the results of molecular docking, the bioactive components from cinnamon were found to be in the same position as the control drugs across the RAS, JAK, and ERK target proteins (Fig. 2). This suggests that these active compounds have a similar ability to interact at the same active site on target proteins

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as the control drug [36,37]. Interestingly, a binding affinity value was established based on the results of molecular docking, which determines whether the active component from Cinnamon has greater potential than the control drugs. Three substances, trans-cinnamyl acetate, trans-alpha-bergamotene, and caryophyllene oxide, were found to have binding affinity values of -6.9, -6.2, and -6.1 kcal/mol for the RAS protein target. However, the stated binding affinity value is still less effective when compared to the control drug, Tipifarnib, which has a binding affinity value of -8.5 kcal/mol.

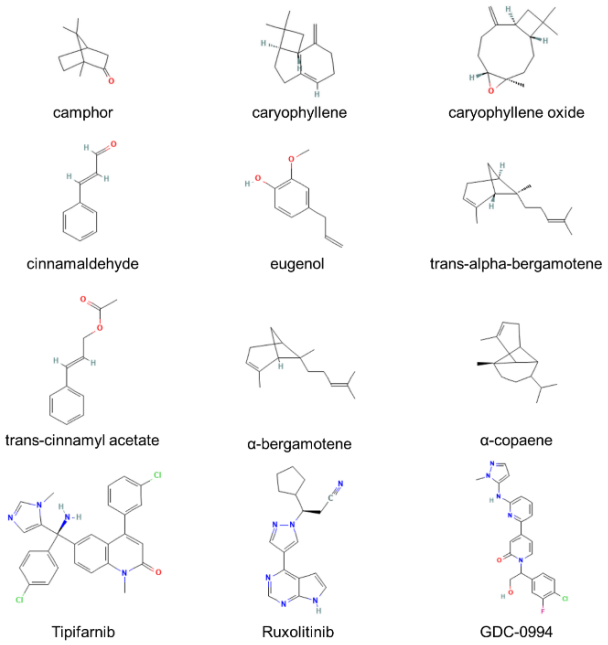

Fig. 1. The 2D structure of ligands used for targeting the RAS, JAK, and ERK protein.

Furthermore, binding affinity values for the JAK protein target were -7.0, -6.9, and -6.7 kcal/mol for three substances, namely caryophyllene, caryophyllene oxide, and α-copaene. Surprisingly, it was discovered that caryophyllene had a higher binding affinity value than the control drug while caryophyllene oxide had the same binding affinity value as the control medication, Ruxolitinib, with a value of -6.9 kcal/mol. Finally, for the ERK protein target, binding affinity values of -7.9, -7.5, and -7.3 kcal/mol were reported for three compounds, namely caryophyllene oxide, caryophyllene, and α-copaene. Similarly to the RAS protein target, the binding affinity value obtained for the ERK protein target is still less favorable when compared to the control medication, GDC-0994, which has a value of -9.4 kcal/mol. Based on the findings from previous studies, it is known that if a molecule has a rising negative binding affinity value, it has a higher proclivity to interact with the target protein [38,39]. As a result, it was discovered in this study that the caryophyllene that interacts with the JAK protein has greater potential than the control drugs due to the fact that has a lower binding affinity value.

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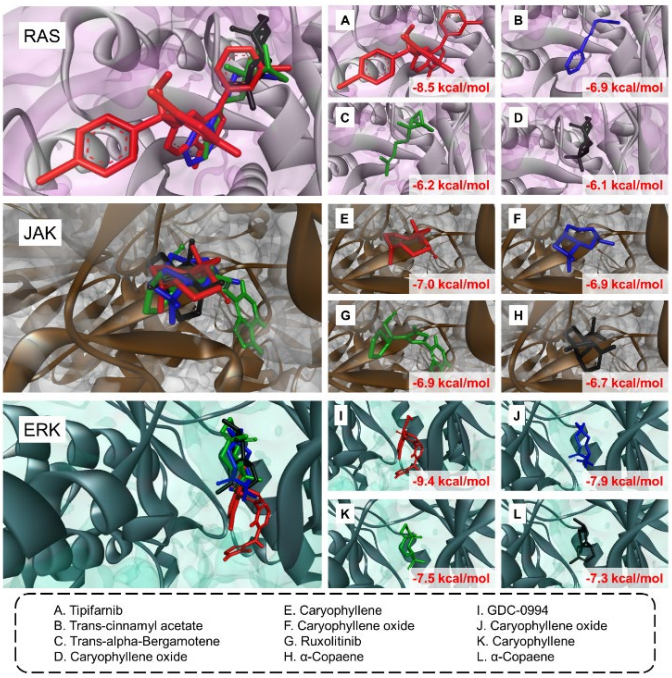

Fig. 2. The 3D structure visualization of protein – ligand complexes after molecular docking. There are three target proteins related to the PDL1 generation signaling including RAS (upper panel), JAK (middle panel), and ERK (lower panel). The number shown in the figure represent the binding affinity value from each ligand to the target protein.

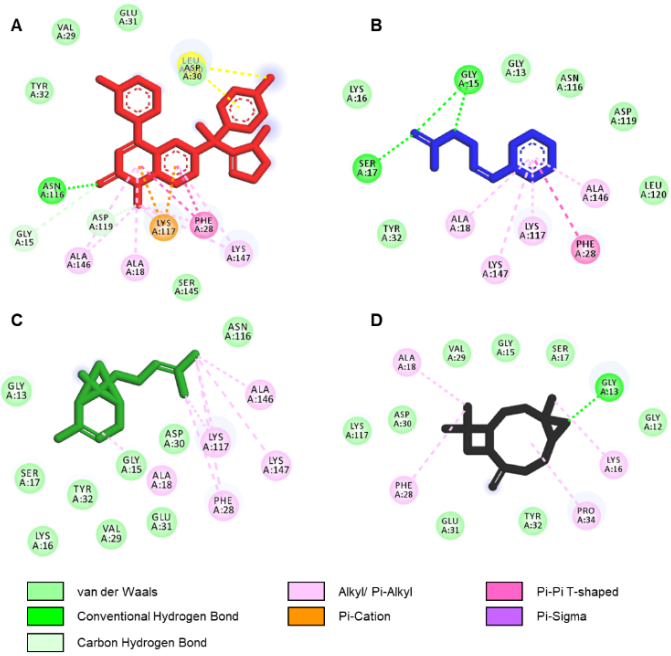

Fig. 3. The 2D structure visualization of ligand interaction to RAS protein after molecular docking. The order of ligand showed in the figure based on the lowest binding affinity score; **(A)** Tipifarnib, **(B)** Trans-cinnamyl acetate, **(C)** Trans-alpha-Bergamotene, and **(D)** Caryophyllene oxide.

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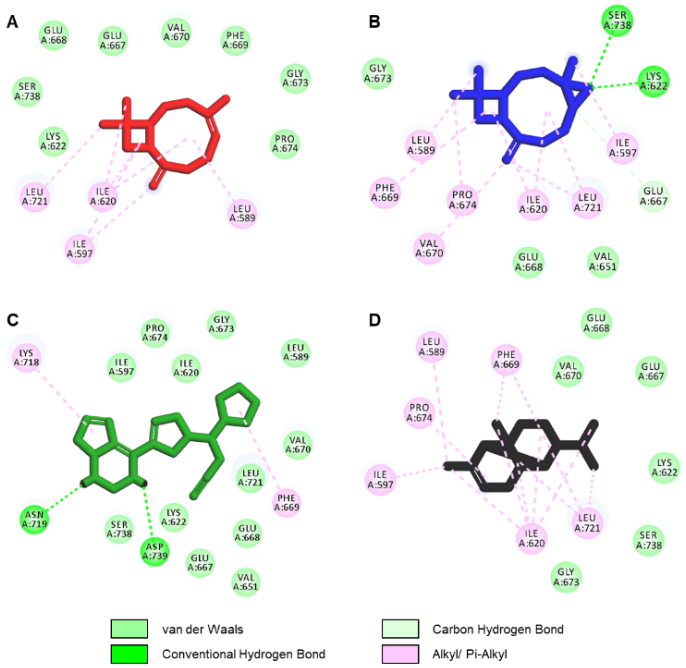

Fig. 4. The 2D structure visualization of ligand interaction to JAK protein after molecular docking. The order of ligand showed in the figure based on the lowest binding affinity score; **(A)** Caryophyllene, **(B)** Caryophyllene oxide, **(C)** Ruxolitinib, and **(D)** α-Copaene.

Furthermore, an overview of the chemical interactions established, and the amino acid residues contained in these interactions is given based on 2D imaging of the protein-ligand complex. Van der Waals, conventional hydrogen bond, carbon hydrogen bond, alkyl/pi-alkyl, pi-cation, pi-pi T-shaped, and pi-sigma chemical interactions have been observed in the RAS protein target (Fig. 3). Meanwhile, various chemical interactions were founded in the JAK protein target, including van der Waals, conventional hydrogen bond, carbon hydrogen bond, and alkyl/pi-alkyl (Fig. 4). Finally, numerous chemical interactions were formed on the ERK protein target, including van der Waals, conventional hydrogen bond, carbon hydrogen bond, unfavorable donor-donor, pi-cation/ pi-anion, pi-sulfur, alkyl/ pi-alkyl, pi-pi T-shaped, and pi-sigma (Fig. 5). Noncovalent interactions, such as electrostatic interactions, salt bridges, or hydrogen bonds, are commonly employed by bioactive compounds and small molecules to bind to proteins [40]. The type of interaction between ligand and protein is particularly essential in drug discovery and development research. The interactions that occur can be beneficial or detrimental. For example, the interaction formed between the ligand and protein can increase the ligand's activity and performance against the target protein, or conversely, it can reduce the effectiveness of the ligand's work and increase the occurrence of side effects [41,42]. Furthermore, each complex of protein-ligand interactions encompasses various amino acid residues. The presence of amino acid residues is particularly crucial in drug discovery and development research since it may determine the strength and weakness of interactions, folding, rigidity, and flexibility of complexes [43,44].

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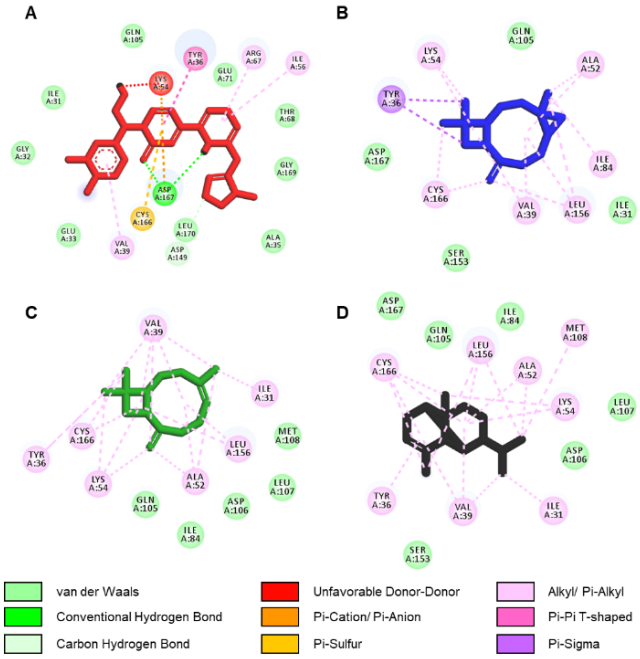

Fig. 5. The 2D structure visualization of ligand interaction to ERK protein after molecular docking. The order of ligand showed in the figure based on the lowest binding affinity score; **(A)** GDC-0994, **(B)** Caryophyllene oxide, **(C)** Caryophyllene, and **(D)** α-Copaene.

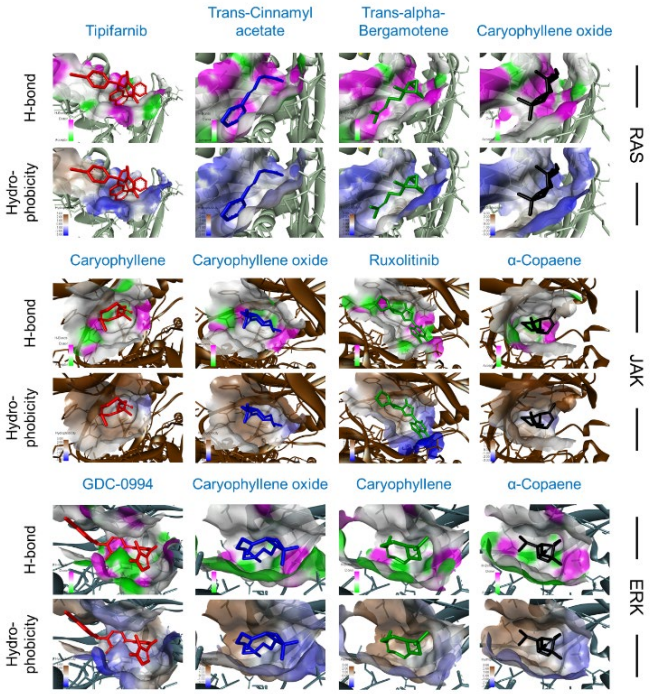

Fig. 6. The physic-chemistry properties of protein – ligand complexes including H-bond and hydrophobicity. RAS (upper panel), JAK (middle panel), and ERK (lower panel).

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In addition, we attempted to investigate and demonstrate the appearance of protein-ligand interactions with H-bond composition and hydrophobicity features (Fig. 6). Commonly, in the interaction of protein-drugs, H-bonds play a critical role. For example, the strength of the H-bond in an interaction influences drug release. A number of variables influence the strength of the H-bond, including the sort of amino acid residue located in the active site and the amount of hydrogen acceptors and donors. The experimental application of hydrogen bonding interactions in drug research has yielded promising outcomes in terms of changing medicinal properties, effectivity of recognition, and drug delivery [45-47]. Thus, in this present study, we assumed that the hydrogen bond in the complex of protein – ligand might become favorable factors that improve the activity of cinnamon bioactive compounds during protein – ligand interaction. It has widely known that hydrophobic forces affect biology and pharmacological activity. In protein structures with open conformations, weak intermolecular interactions like hydrogen bonding and hydrophobic interactions stabilize energetically-favored ligands. More important, precision hydrophobicity measurements and hydrophobic interaction estimations may significantly impact protein folding and side chain orientation models. Improved modeling and depiction of hydrophobic interactions may assist to elucidate biological phenomena like efflux-induced medication resistance [48,49].

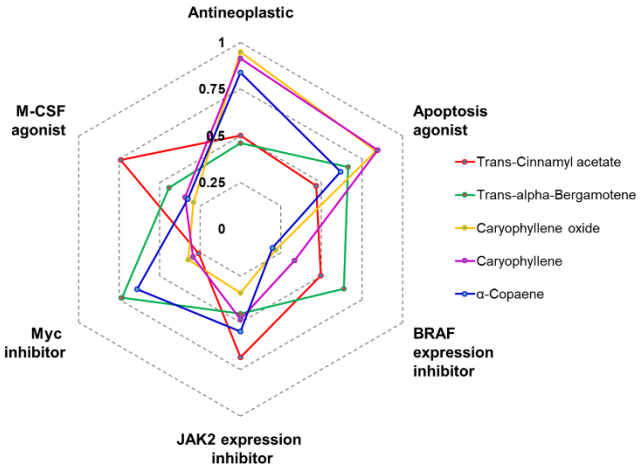

Fig. 7. The biological activities prediction of *Cinamon* bioactive compounds. The predicted biological activities measured are related to the anti-cancer progression which include antineoplastic, apoptosis agonist, BRAF expression inhibitor, JAK2 expression inhibitor, Myc inhibitor, and M-CSF agonist.

Moreover, we predicted the biological activity of bioactive compounds derived from cinnamon (Fig. 7). By employing this biological activity prediction method, it is possible to ascertain the propensities and potential of these active compounds as viable substitute therapies for specific diseases. Several parameters with anti-cancer hallmarks were employed in this work, including antineoplastic, apoptosis agonist, BRAF expression inhibitor, JAK2 expression inhibitor, Myc inhibitor, and M-CSF agonist [50,51]. A number of compounds with prominent potential for various parameters were obtained according to our *in silico* study. Caryophyllene oxide, caryophyllene, and α-copaene, for example, have a high antineoplastic potential. Caryophyllene and caryophyllene oxide are powerful apoptosis inducers. Trans-alpha-bergamotene and trans-cinnamyl acetate have the ability to suppress BRAF expression. JAK2 expression inhibitors comprise trans-cinnamyl acetate, α-copaene, and caryophyllene. Trans-alpha-bergamotene and α-copaene have the potential to be dominant as Myc inhibitors, while very few substances operate as M-CSF agonists, with only trans-cinnamyl acetate having a high Pa value when compared to other drugs which indicates the other compounds exerts the anti-M-CSF activation properties.

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Conclusions

In accordance with the results of biological activity predictions, it was discovered that cinnamon's active compounds contribute as cancer fighting agents by having high Pa values for several parameters such as antineoplastic, apoptosis agonist, BRAF expression inhibitor, JAK2 expression inhibitor, and Myc inhibitor also low Pa values contrary to M-CSF agonists. On top of that, molecular docking experiments revealed that caryophyllene compounds have higher binding affinity for JAK as a protein target than other compounds, including control drugs. Even though the cinnamon compounds did not possess more affinity for binding than the control drugs on the RAS and ERK protein, a larger investigation such as structure modification and molecular dynamic simulations remains required.

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