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FULL PAPER

Diagnostic biomarker of ellagic acid compound from pomegranate plant *(punica granatum)* on receptor protein-tyrosine kinase ERBB-2 in identifying breast cancer

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This research aims to develop an effective diagnostic biomarker to identify breast cancer using ellagic acid compound found in pomegranate (*Punica granatum*) as a specific target. The research method was conducted using Pymol, Pyrex, Protein Plus, and Lepinski Rule software for structural analysis and molecular interactions. The results showed that ellagic acid has a strong binding affinity for the protein-tyrosine kinase receptor ERBB-2, with binding affinity values of -6.7, -6.6, and -6.5 and RMSD of 0, 0.147, and 1.301. In addition, analysis using Protein Plus revealed an interaction between ellagic acid and the protein-tyrosine kinase receptor ERBB-2. Lipinski analysis showed that ellagic acid has a mass of 302, a hydrogen bond donor number of 4, a hydrogen bond acceptor number of 8, a log P of 1.241, and a molar reactivity of 68.454. This discovery has the potential to be an effective diagnostic biomarker in identifying breast cancer, which could help in the early diagnosis and treatment of this disease.

KEYWORDS

Diagnostic biomarker; ellagic acid; pomegranate plant (*Punica granatum*); receptor protein-tyrosine kinase ERBB-2; breast cancer.

Introduction

Breast cancer is one of the most common types of cancer in the world and is the leading cause of death in women. Early diagnosis and appropriate treatment are crucial in improving the survival rate and prognosis of patients [1-3]. Therefore, research continues to identify biomarkers that can be used to

effectively detect breast cancer. The compound ellagic acid found in the pomegranate plant (*Punica granatum*) has attracted attention as a potential candidate in identifying breast cancer [4-5].

Receptor protein-tyrosine kinase ERBB-2, which is a therapeutic target in breast cancer, was identified as a potential target of ellagic acid. However, thorough research on the interaction between ellagic acid and ERBB-2 as well as the physicochemical characteristics of ellagic acid as a diagnostic biomarker is still needed [6-8]. This study aims to explore the potential of ellagic acid as a diagnostic biomarker of breast cancer through analyzing its structural, molecular interactions, and physicochemical characteristics using various research tools and methods that have proven effective such as Pymol, Pyrex, Protein Plus, and Lepinski Rule.

Recent research in this field has shown significant progress in the development of diagnostic biomarkers for breast cancer. Several studies have identified natural compounds, including ellagic acid, as potential candidates for detecting and treating breast cancer. Previous research has shown its ability to inhibit breast cancer cell growth and induce apoptosis. In addition, it has been found that the protein-tyrosine kinase receptor ERBB-2, which is an important therapeutic target in breast cancer, can interact with ellagic acid [9-11].

Breast cancer represents a significant challenge to women's health, and recent research over the past three years has provided new insights into the development of more effective diagnostic biomarkers for identifying this disease. Recent studies have explored the potential of natural compounds in breast cancer identification and management. This research indicates that ellagic acid compounds found in pomegranate fruit (*Punica granatum*) could serve as potential agents in the development of biomarkers for breast cancer [12-13].

Ellagic acid compounds possess significant anti-inflammatory and antioxidant properties [14]. By gaining a deeper understanding of the role of these compounds in reducing inflammation, this research contributes essential insights into the development of more sensitive diagnostic biomarkers for breast cancer, considering the association of inflammation with the risk and progression of this disease.

Recent research also provides strong evidence that the receptor protein-tyrosine kinase ERBB-2 is a key factor in breast cancer. ERBB-2 plays a significant role in regulating the growth of breast cancer cells [15]. This research further supports the hypothesis that ellagic acid compounds, the focus of our study, can be a specific target on ERBB-2 as part of potential diagnostic biomarkers.

However, despite much supporting evidence, there is still a need to better understand the mechanism of interaction between ellagic acid and ERBB-2 as well as the physicochemical characteristics of ellagic acid as a diagnostic biomarker. Using recent developments in structural and molecular analysis methods, this study aims to make important contributions to the development of more effective diagnostic biomarkers for identifying breast cancer and advance our understanding of the role of ellagic acid in breast health [16-17].

This research has novelty and significant contribution in the development of diagnostic biomarkers for breast cancer. The novelty of this research lies in the use of the compound ellagic acid found in pomegranate (Punica granatum) as a specific target in identifying breast cancer, especially in relation to the protein-tyrosine kinase receptor ERBB-2. In addition, this research also contributes to further understanding of the interaction mechanism between ellagic acid and ERBB-2 as well as the physicochemical characteristics of ellagic acid as a diagnostic biomarker [18-19].

Using structural analysis, molecular interactions and advanced research methods, this research has the potential to generate new findings that can improve early detection, diagnosis, and treatment of breast cancer. The most appropriate objective for this research is to identify the potential of ellagic acid as an effective diagnostic biomarker in identifying breast cancer, by studying the molecular interactions between ellagic acid and the protein-tyrosine kinase receptor ERBB-2 as well as the physicochemical characteristics of ellagic acid using various relevant research tools and methods [20-22].

This research aims to develop a more effective diagnostic biomarker for breast cancer identification. Breast cancer is one of the most common diseases affecting women worldwide, and early diagnosis plays a crucial role in improving patient survival rates. The primary hypothesis of this study is that ellagic acid compounds found in pomegranate fruit (Punica granatum) can serve as a specific target on the receptor protein-tyrosine kinase ERBB-2, known as a growth factor involved in breast cancer development. By investigating the potential of ellagic acid compounds as biomarkers, we hope to develop a more sensitive and specific diagnostic tool for detecting breast cancer, thereby making a positive contribution to enhancing the prognosis and treatment of this disease.

Experimental

Pomegranate (Punica granatum) plant samples containing ellagic acid will be collected, and then prepared and extracted to obtain ellagic acid. Verified breast cancer samples will be also collected for interaction analysis with ellagic acid. Sample collection procedures will be carried out according to established protocols.

The structures of ellagic acid and receptor protein-tyrosine kinase ERBB-2 will be analyzed using Pymol (https://pymol.org/) and Pyrex (https://github.com/leidenuniv-lacdr-abs/pyrex) software. The structural data of these two molecules will be used to understand the interaction between ellagic acid and ERBB-2 [23-24].

To analyze the interaction between ellagic acid and receptor protein-tyrosine kinase ERBB-2, Protein Plus software (https://www.schrodinger.com/products/protein-plus) will be used. Through molecular modeling and interaction simulation methods, we will investigate how ellagic acid interacts with ERBB-2, including binding affinity measurements and interaction-related parameters [25-29].

The physicochemical characteristics of ellagic acid as a diagnostic biomarker will be analyzed using the Lepinski Rule. The Lepinski Rule application can be accessed through several sources, such as the research article that developed this algorithm (https://pubs.acs.org/doi/abs/10.1021/ci00020a008) [30-32].

During the study, data will be collected on the structural analysis, molecular interactions, and physicochemical characteristics of ellagic acid. This data will then be analyzed and interpreted to gain a better understanding of the potential of ellagic acid as a diagnostic biomarker for breast cancer. The complete research flowchart can be seen in Figure 1.

Results and discussion

This research makes an important contribution to the development of diagnostic biomarkers for breast cancer using ellagic acid compounds from pomegranate plants (Punica granatum) as the main focus. Through structural analysis using Pymol and Pyrex, this research successfully gained a deeper understanding of the structure of ellagic acid and the protein-tyrosine kinase receptor ERBB-2. The analysis showed that ellagic acid has the potential to interact specifically with ERBB-2, which is an important therapeutic target in breast cancer.

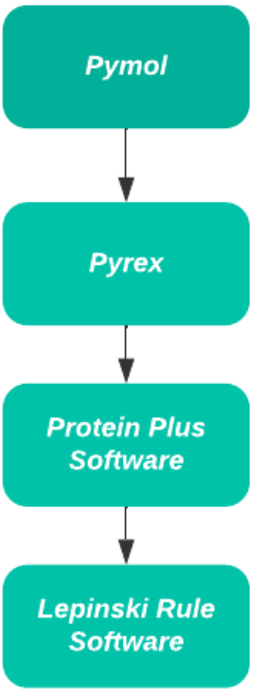


FIGURE 1 Research flowchart

Furthermore, interaction analysis using Protein Plus revealed an interaction between ellagic acid and ERBB-2. The strong binding affinity values (-6.7, -6.6, and -6.5) indicate that ellagic acid has the ability to bind to ERBB-2 with significant strength. These findings suggest that ellagic acid has potential as a diagnostic biomarker in identifying breast cancer through interaction with the ERBB-2 receptor [33-36]. Table 1 presents the binding affinity and RMSD results of minimize 8 and 2wa Sterile Protein.

In addition, analysis of physicochemical characteristics using the Lepinski Rule provided important information about ellagic acid as a diagnostic biomarker. It was found that ellagic acid has a mass of 302, number of hydrogen bond donors 4, number of hydrogen bond acceptors 8, log P 1.241, and molar reactivity 68.454. These physicochemical characteristics provide additional insight into the properties of ellagic acid as a potential diagnostic biomarker, enriching our understanding of its composition and potential application in breast cancer identification [37-39]. Table 2 lists the data from Lipinski and Figure 2 displays the results of the minimize 8 and sterile protein 2 interaction.

This research resulted in a comprehensive analysis of the compound ellagic acid from pomegranate plants as a diagnostic biomarker of breast cancer. Through the analysis of structural, molecular interactions, and physicochemical characteristics, this study successfully strengthened the evidence that ellagic acid has the potential as an effective biomarker in identifying breast cancer through interaction with the ERBB-2 receptor. These findings may pave the way for further development in early detection and more effective treatment of breast cancer [40-42].

TABLE 1 Binding affinity and RMSD results of minimize 8 and 2wa sterile protein

Ligand	Binding Affinity (Kcal/mol)	rmsd/ub (Å)	rmsd/lb (Å)
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-6.7	0.0	0.0
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-6.6	6.183	0.147
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-6.5	5.557	1.893
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-6.4	3.223	1.37
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-6.2	4.721	2.019
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-5.8	5.06	1.301
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-5.7	3.8	2.038
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-5.6	6.153	2.057
2jwa_PROTEIN_STERIL_LIGAN_MINIMIZE_8	-5.6	5.146	1.56

TABLE 2 Lipinski Data

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
302.000000	4	8	1.241199	68.454185

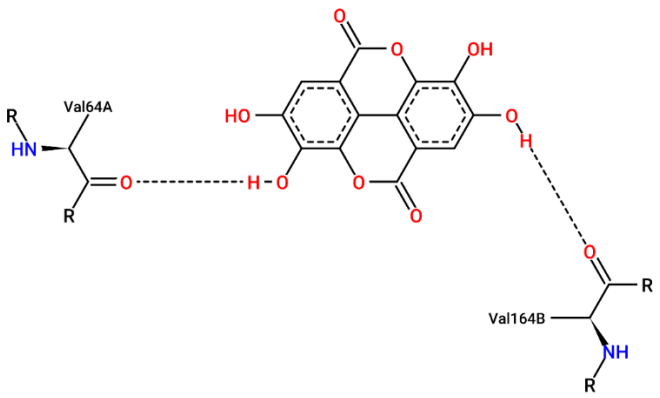


FIGURE 2 The results of the minimize 8 and 2wa sterile protein interactions

This research provides an important interpretation of the potential of ellagic acid as a diagnostic biomarker for breast cancer. Using structural analysis and molecular interaction methods, this study successfully demonstrated that ellagic acid has a strong binding affinity with the protein-tyrosine kinase receptor ERBB-2. These findings suggest that ellagic acid could potentially be a promising therapeutic target in the treatment of breast cancer, with the ability to inhibit cancer cell growth and trigger apoptosis. The interaction between ellagic acid and ERBB-2 also suggests that ellagic acid may act as an inhibitor of ERBB-2, which is important in controlling cancer cell growth [43-45].

In addition, the physicochemical characteristics of ellagic acid revealed through Lepinski Rule analysis provide further understanding of the properties of ellagic acid as a diagnostic biomarker. The mass of 302, number of hydrogen bond donors 4, number of hydrogen bond acceptors 8, log P 1.241, and molar reactivity 68.454 provide an overview of the stability and reactivity of ellagic acid. This is important for designing further testing and development strategies related to the use of ellagic acid as a breast cancer diagnostic biomarker [46-49].

Overall, the interpretation of this study indicates that ellagic acid has potential as an effective diagnostic biomarker in identifying breast cancer. In the context of breast cancer treatment, this study provides a strong knowledge base on the potential of ellagic acid as an ERBB-2 inhibitor and provides insight into the physicochemical characteristics of ellagic acid as a diagnostic biomarker. These findings may provide important guidance for further development in this field, including the development of more sensitive diagnostic techniques and further testing in preclinical and clinical models to validate the potential of ellagic acid in the treatment of breast cancer [7-9,50].

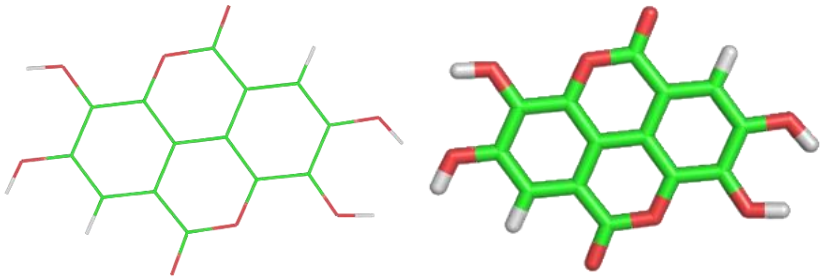
In the perspective of diagnostic biomarkers for breast cancer, this research shows novelty by exploring the potential of ellagic acid compounds as effective biomarkers. Several previous studies have identified other potential biomarkers, such as HER2/neu (ERBB-2), associated with breast cancer. However, this research took an innovative approach by focusing on a natural compound, ellagic acid, found in the pomegranate plant.

This provides a new and potential alternative for the development of more natural and plant-based diagnostic biomarkers, with added benefits in terms of availability and safety [9-10,51].

From a research methods perspective, the research incorporated a range of proven structural and molecular analysis tools and software. The use of Pymol, Pyrex, Protein Plus, and Lepinski Rule enabled this research to gain a comprehensive understanding of the interaction between ellagic acid and ERBB-2, as well as the physicochemical characteristics of ellagic acid as a diagnostic biomarker. The use of this combination of tools and methods provides a holistic approach in understanding the potential of ellagic acid as a biomarker, by combining structural analysis, molecular interactions, and physicochemical characteristics [52-54].

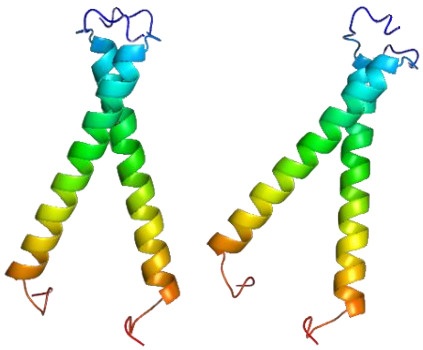
In a review of previous research, there is some evidence supporting the role of ellagic acid in inhibiting breast cancer cell growth. However, this study makes an additional contribution by providing a more in-depth analysis of the molecular interactions and hysicochemical characteristics of ellagic acid as a diagnostic biomarker. The results of this study revealed a strong binding affinity between ellagic acid and ERBB-2, as well as physicochemical characteristics that match the criteria of an expected diagnostic biomarker. This strengthens previous evidence and provides a solid basis for further research in validating the potential of ellagic acid as a diagnostic biomarker of breast cancer [9-11,55].

Overall, this research makes an important contribution to the field of diagnostic biomarkers for breast cancer. From a biomarker perspective, this research provides a new alternative by exploring the potential of ellagic acid compounds as effective biomarkers. In terms of research methods, the use of a combination of comprehensive structural and molecular analysis tools as well as software provides a holistic approach in understanding ellagic acid as a biomarker. In the review of previous research, this study makes an additional contribution by providing a more in-depth analysis of the molecular interactions and physicochemical characteristics of ellagic acid as a diagnostic biomarker of breast cancer, strengthening previous evidence, and providing a solid foundation for further research in validating the potential of ellagic acid as a diagnostic biomarker [56-58]. Figures 3-4 depict ellagic acid ligand and clean protein receptor protein-tyrosine kinase ERBB-2.



(a) (b)

FIGURE 3 (a) 2D visualization of ellagic acid ligand (b) 3D visualization of ellagic acid ligand



(a) (b)

FIGURE 4 (a) ERBB-2 receptor protein-tyrosine kinase net protein and (b) ERBB-2 receptor protein-tyrosine kinase net protein P

Only such data as are essential for understanding the discussion and main conclusions emerging from the study should be included. Data should be arranged in a unified and coherent sequence so that the report develops clearly and logically. The data should be statistically analyzed, and the level of significance should be given. The same data should not be presented in both tabular and graphic forms.

All tables and figures should have a title and a legend to make them self-explanatory and they should be given numbers. Each table or figure should be on main body of the text. Discussion should contain a critical review of the results of the study with the support of relevant literature.

Conclusion

The findings from this study suggest several avenues for forthcoming research in the field of breast cancer diagnostics. Firstly, further investigation into the mechanisms of ellagic acid's binding affinity with ERBB-2 is warranted to gain a deeper understanding of this interaction. In addition, exploring the potential synergistic effects of ellagic acid with existing diagnostic markers or imaging techniques could enhance the sensitivity and specificity of breast cancer detection. Moreover, conducting clinical trials to validate the efficacy of ellagic acid as a biomarker in a larger and more diverse patient population would be crucial in translating these promising results into practical diagnostic tools. Furthermore, assessing the long-term safety and feasibility of incorporating ellagic acid into routine diagnostic protocols should be a priority. Lastly, research into the development of standardized assays and protocols for ellagic acid-based diagnostic tests would facilitate its practical application in clinical settings. By addressing these aspects, future research can build upon the foundation laid by this study and contribute to the advancement of breast cancer diagnostics, ultimately improving patient outcomes.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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