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Screening of Rhodomyrtus tomentosa (Aiton) Wight (Karamunting) Compounds that Have the Potential for Breast Cancer

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Abstract

Breast cancer is the highest disease in the world beating lung cancer, so various alternatives are needed to find a treatment. Screening drug discovery against breast cancer by targeting BCL-2 occupies the main position and is the goal of this study. The method used is insilico. the material used is 10 compounds from R. tomentose, 2w3l protein from RCSB, PLANT docking software, the docking coordinate used is X: 39.8057 Y: 26.9355 Z: -12.4145 with a radius of 11.1871, then to find out the type of bond and residue involved using discovery studio. The results of this study were docking scores from -91.3871(5'-Desgalloylstachyurin) to -65.4754 (Afrormosin), activity predictions from PASS online from 0.174 (Rhodomyrtosone C) to 0.799 (Lupeol). Based on the docking score, three compounds that have the potential to inhibit the work of BCL-2 were obtained namely 5'-Desgalloylstachyurin, Rhodomyrtosone B and Rhodomyrtosone D.

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INTRODUCTION

Breast cancer is a disease that is often diagnosed than other types of cancer in the world (Wilkinson &; Gathani, 2022). It is estimated that new breast cancer cases reached 2.3 million in 2020, accounting for 11.7% of all new cancers, and 684,996 cases died from it (Sung et al., 2021). Female breast cancer patients in China estimated 306,000 new cases in 2016 (Zheng et al., 2022). The incidence of breast cancer has increased since the widespread use of mammography screening and continues to increase as the population ages. In most western countries, breast cancer death rates have declined in recent years, due to modern treatment strategies and early detection. In China, breast cancer ranks first among the causes of cancer death in women aged 15-44 years, and there is still an increasing trend of mortality from breast cancer (Allemani et al., 2015).

The difference in incidence by age between China and western countries. In western populations, only about a quarter of breast cancers are diagnosed before age 50, and only <5% before age 35. In China, about two out of three are diagnosed between the ages of 40 and 59. Differences were also seen with the average value of age. The average age of diagnosis for Chinese breast cancer is 49, which is very different from western countries, where the average age of diagnosis is 60 (Australia) and 61 (US), respectively (Autier et al., 2010). Major risk factors for breast cancer include: reproductive and hormonal risk factors

(early age at menarche, advanced age at menopause, advanced age at first delivery, fewer children, less breastfeeding, menopausal hormone therapy, and oral contraceptives), lifestyle risk factors (overweight, physical activity, and alcohol intake) (McTiernan, 2003) . Male breast cancer accounts for 1% of all breast cancer cases. Family history and genetic predisposition, hormonal imbalances caused by clinical disorders (such as gynecomastia and cirrhosis), and radiation exposure can contribute to the occurrence of breast cancer in men (Chen & Parmigiani, 2007). With the occurrence of breast cancer, alternative treatments sourced from nature are needed. One plant (Inayah et al., 2022) that has potential in the treatment of breast cancer is karamunting.

Karamunting has the Latin name *R. tomentosa is a* plant that is often used by the community either for fruit or medicine. The fruit of this plant is purple so that it has the potential as an antioxidant and antioxidant activity, this has been proven by research conducted by Salampe with IC_{50} of 24.45 ppm and cytotoxic using the BSLT method of 31.80 ppm (Salampe et al., 2020). R. tomentosa has antibacterial ability with MIC 3.66 ppm against *S. aureus* in hexane n fraction and 1.83 ppm in ethyl acetate fraction (Liu et al., 2016). As immunomodulators it induces changes in the expression of proinflammatory cytokines (IL1β, IL8, and TNFα), anti-inflammatory cytokines (IL10 and tgfβ), inducible enzymes (inos, cox2, and arginase), and antioxidant enzymes (gpx1). Co-exposure of *R. tomentosa* with LPS resulted in a reduction in the expression of genes associated with inflammatory processes (IL1β, IL8, TNFα, INOS, SAA, hepcidin, and gpx1), suggesting anti-inflammatory effects. Similarly, co-exposure to rhodomyrtone with LPS led to downregulation of inflammation-related genes (IL1β, INOS, SAA, and hepcidin) (Na-Phatthalung et al., 2018).

Apoptosis is an important mechanism in overcoming breast cancer, therefore the proteins involved in apoptosis are important to be inhibited. The signal pathway against BCL-2 in this study is a target that needs to be inhibited. As far as researchers know, there has been no screening of compounds from R. tomentosa against BCL-2. The novelty of this study is the in silico screening of compounds from R. Temontosa against BLC-2. The purpose of this study is to look for compounds that have potential as BCL-2 inhibitors.

METHOD

The equipment used in this research is AspireES14, the software used is PLANT, Discovery studio (Systèmes, 2020), Yasara. The materials used are ten compounds contained in *R. tomentosa* and Bcl2-xL protein obtained from RSCB with the code 2w3l with a resolution of 2.10 Å (Berman et al., 2000), homosapiene organisms, x-ray difraxtion method.

The study began by extracting structural data of compounds contained from *R. tomentosa*, the compounds obtained were then stored in smile and mol2 modes for the purposes of activity prediction analysis using PASSonline (Lagunin et al., 2000) and docking using PLANT (Korb et al., 2009) . The 2w3l protein obtained from RCSB removed water molecules and selected one of the chains used, in this study using proteins on the A chain bound to native ligands. Docking begins by redocking the native ligand to obtain coordinates and radii that have an RMSD below 2 Å. After getting the exact coordinates and radius, these coordinates and radius are used for docking the compounds contained in *R. tomentosa* (C et al., 2022).

The data analysis is a comparative docking system against a native ligand with the code CHEMB503454, because this docking score indicates the ease of interaction, the more negative energy the easier the reaction occurs (Xavier et al., 2016).

RESULTS AND DISCUSSION

Apoptosis is a regulated form of cell death triggered in response to developmental cues or cellular stress. This selective cell suicide plays an important role in various physiological and pathological processes including development, immunity and disease where the removal of damaged or excessive cells helps ensure the health of the organism (Meier et al., 2000). There are two apoptotic pathways: the extrinsic pathway (activated by the binding of cell surface death receptor ligands) and the intrinsic pathway (mitochondria) (Oltersdorf et al., 2005). This review focused on the BCL-2 family of proteins that regulate activation of the intrinsic apoptosis pathway in response to cellular stresses such as DNA damage, γ irradiation, activation of oncogenes, and growth factor withdrawal. Recent drug discovery advances have enabled specific targeting of BCL-2 (B-cell lymphoma 2) (Souers et al., 2013). So that the screening of compounds that have the potential to be BCL-2 inhibirors. The approach in this study through in silico testing using the PLANTS docking method because insilico research is a screening with a relatively fast time to obtain potential compounds, so that in the end it can reduce experiments both in vitro and in vivo on samples of compounds that are less efficacious, and another advantage is software that is used free of charge

The algorithm used in the PLANTS method uses the ant colony principle (Korb et al., 2009). The study began with redocking the native ligand and validating the coordinates used for docking. Docking validation used by superimposing 2w3l protein and ligand-protein complex (Laela et al., 2022) redocking results. The RMSD obtained is 1.76 Å, thus meeting the docking validation requirement of below 2 Å (Rodríguez et al., 1989). The coordinates used in this redocking are X:39.8057 Y:26.9355 Z:-12.4145 and the radius used is 11.1871. So these coordinates are used for redocking *R. tomentosa compounds.* The results of docking can be seen in table 1 so that the top 5 compounds have the best score of this compound there is 5'-Desgalloylstachyurin; Rhodomyrtosone B; Rhodomyrtosone D; Pedunculagin; Rhodomyrtosone C, when compared with native ligands, has an ability of 85.37%; 74,78%; 74,77%; 74.59% and 71.83%. The % comparative value is greater than the docking score value which is increasingly negative, so this compound is easy to react because the energy is lower (Jain &; Nicholls, 2008).

Table 1. Docking Score

Compound	Docking score
native	-107.048
5'-Desgalloylstachyurin	-91.3871
Rhodomyrtosone B	-80.056
Rhodomyrtosone D	-80.0479
Pedunculagin	-79.8564
Rhodomyrtosone C	-76.8982
Rhodomyrtosone A	-75.1483
Lupeol	-73.035
Rhodomyrtone	-68.0153
Tomentosin	-66.7477
Afrormosin	-65.4754

Based on activity predictions using PASSonline, five top-ranked compounds were obtained, namely Lupeol (0.799); Afrormosin (0.546); 5'-desgalloylstachyurin(0.382); Tomentocin (0.332) and Rhodomyrtone (0.312). The best score is lupeol with a value above 0.7 so that this senjiwa is potent in the treatment of breast cancer both on a laboratory scale (invitro or vivo test) and in silico. While afformosin 5'-desgalloylstachyurin; Tomentosin;

Rhodomyrtone, the value is above 0.3 but below 0.7 so that this compound has only been tested insicilo and has not been proven in wet laboratories (Lagunin et al., 2000).

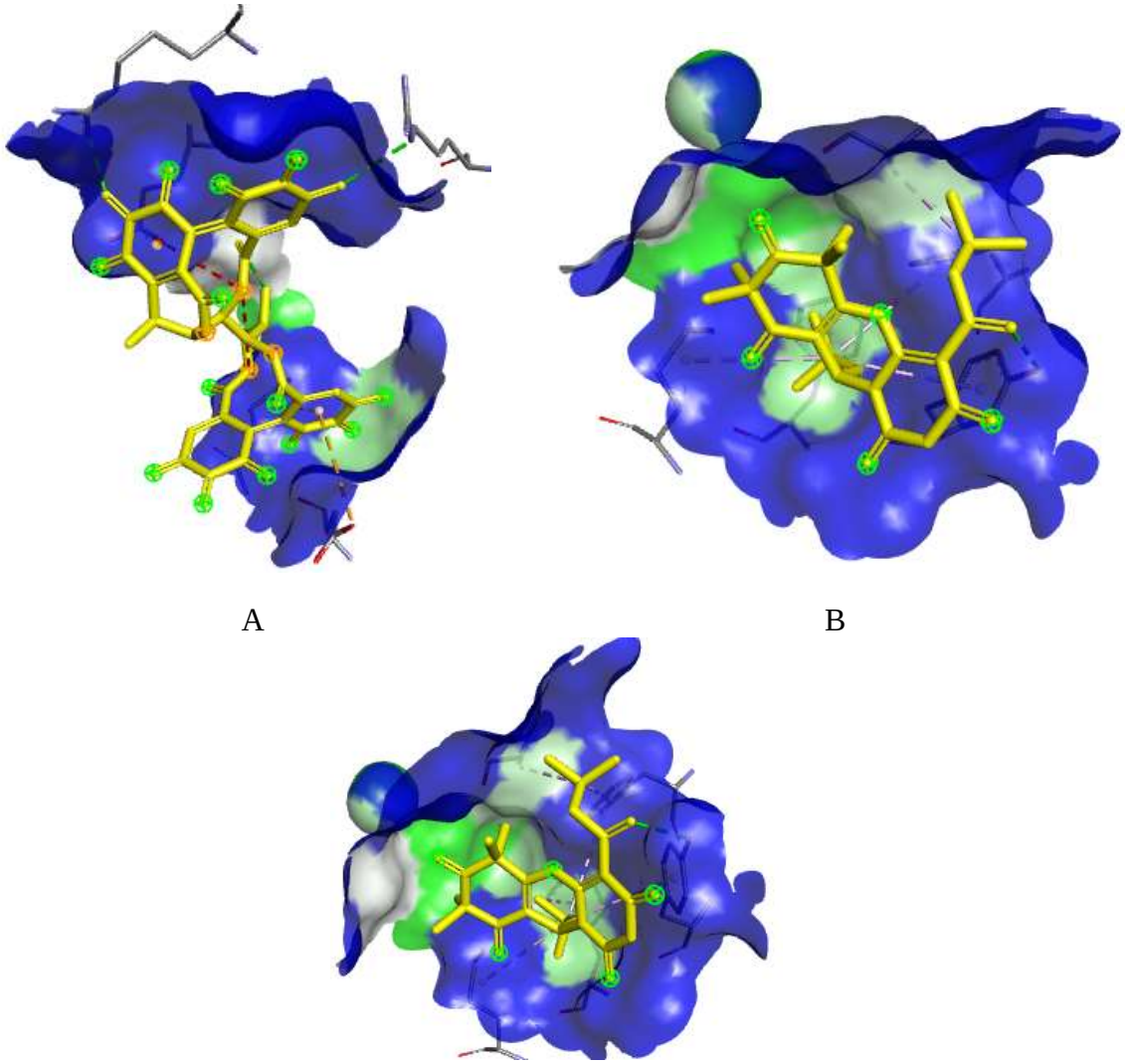
Table 2. Activity predictions

Compound	Pa	Pi
5'-Desgalloylstachyurin	0,382	0,035
Rhodomyrtosone B	0,213	0,088
Rhodomyrtosone D	0,213	0,088
Pedunculagin	0,287	0,059
Rhodomyrtosone C	0,174	0,112
Rhodomyrtosone A	0,200	0,094
Lupeol	0,799	0,004
Rhodomyrtone	0,312	0,120
Tomentosin	0,332	0,046
Afrormosin	0,546	0,015

Table 3. Interaction of compounds with amino acid residues

Compound	Types of bonding		
	Hydrogen	electrostatic	hydrofobic
native	ARG105; LEU96; GLU95	ASP70	TYR67; PHE71; PHE63; ALA108
5'-Desgalloylstachyurin	ARG98; ARG105	ASP70; GLU95	MET74
Rhodomyrtosone B	TYR67		PHE71; ALA108; MET74; PHE63
Rhodomyrtosone D	TYR67	-	PHE71; ALA108; MET74; PHE63
Pedunculagin	TYR67; ASN102; ARG105; LEU96	ASP70	ARG105
Rhodomyrtosone C	ARG105	-	TYR67; LEU96
Rhodomyrtosone A	TYR67	-	ALA108; PHE63; PHE71
Lupeol	-	-	LEU96; ALA108; MET74; VAL92; PHE63; TYR67; PHE71; PHE112
Rhodomyrtone	-	-	TYR67
Tomentosin	TYR67	-	PHE71; ALA108; MET74; VAL92; LEU96; PHE63
Afrormosin	TYR67; ASN102	-	MET74; PHE71; ARG105; ALA108

The equation of interacting residues can be seen in Table 3. The five compounds that have the most residual equations are Pedunculagin (50%); Tomentocin (62.5%); Lupeol (62.5%), Rhodomyrtosone A (50 %) and Rhodomyrtosone B and D (50%). The same residual pedunculagin as the native ligand are TYR67, ARG105, LEU96 and ASP70. Similar tomentosin residues are TYR67, PHE71, ALA108, LEU96 and PHE63. The same residual lupeol is LEU96; ALA108; PHE63; TYR67 and PHE71. Rhodomyrtosone A residues are TYR67, ALA108, PHE63 and PHE71. Rhodomyrtosone D residues are TYR67, PHE71, ALA108 and PHE63. This similarity of interacting residues indicates that the chromophores of the ligand have chromophore resemblance to the native ligand (Cournia et al., 2017)



A B

C

Figure 1. Visualization of the interaction between ligand and BCL-2 protein, yellow color is ligand, blue color ability between ligand and protein is relatively high, green color interaction between ligand and protein is relatively low. A: 5'-desgalloylstachyurin; B: Rhodomyrtosone B and C: Rhodomyrtosone D.

Based on the docking score, the top three compounds and interacting residues can be seen in Figure 1. 5'-Desgalloylstachyurin, Rhodomyrtosone B and Rhodomyrtosone D do not have the same residual equation if compartmentally with the native ligand, this is likely to cause the scor docking distance to be 11.3 and 5'-Desgalloylstachyurin occupies the most stable position (Febriani et al., 2022). The most important residues in this interaction are ARG105, ASP70 and GLU95 because in these residues hydrogen bonds occur and electrostatic bonds so that there is hydrogen transfer between ligand and protein and ease of interaction between ligand and protein because there is a difference in positive and negative charges so that electromagnetic bonds occur (Porter et al., 2009).

CONCLUSION

Based on screening of BCL-2 protein inhibitors from *R. tomentosa* compounds that have potential insilico for the treatment of breast cancer are 5'-Desgalloylstachyurin, Rhodomyrtosone B and Rhodomyrtosone D, so that these three compounds can be carried out

further tests both in vitro and in vivo and other compounds can be abandoned because the results of the study are less potential as BCL-2 inhibitors.

RECOMMENDATIONS

This research has limitations, so to provide more accurate results it is necessary to do invitro and in vivo tests.

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