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Original Research Article

In Silico Study of the Potential of Garlic Allicin Compound as Anti-Angiogenesis in Breast Cancer

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ABSTRACT

The angiogenesis process in breast cancer has an important role in the development of tumors, metastases, and is also associated with a decrease in breast cancer patients' survival. Vascular endothelial growth factor receptor 2 (VEGFR-2) plays a major role in the angiogenesis process. VEGFR-2 inhibition is expected to ably inhibit breast cancer cells growth, especially triple-negative breast cancer. Allicin from single garlic has an antioxidant and anticarcinogenic effect similar to N-Acetyl Cysteine (NAC). This study aims to evaluate Allicin compound from single garlic as an angiogenic potential inhibitor of VEGFR-2 breast cancer through an *in silico* study. The study used ChemDraw Professional 16.0 program, Chem 3D 16.0, and Molegro Virtual Docker-5. VEGFR-2 receptor used in this study was with PDB code: 4ASD, which had a native ligand Sorafenib (BAX_1500). Data analysis were performed by comparing the binding energy of the VEGFR-2 receptor with Allicin and NAC ligands as Rerank Score. Absorption, Distribution, Metabolism, and Excretion (ADME) and toxicity of compounds were tested using pkCSM online tool program. The results of re-docking process showed that the Root Mean Square Deviation (RMSD) was less than 2 (0.868). The *in silico* test showed that Allicin had lower anti-angiogenesis potential than NAC (Bond energy: Sorafenib: -155.145 Kcal/mol, Allicin: -54.2265 Kcal/mol, and NAC: -57.5174 Kcal/mol). However, the safety profile test using pkCSM online tool showed that Allicin had a better profile than NAC, both in pharmacokinetics and toxicity. In conclusion, the Allicin compound from single garlic is an angiogenic potential inhibitor of VEGFR-2 breast cancer through an *in-silico* study.

***Keywords*:** *Allicin, In silico, Anti-angiogenesis, Breast cancer*.

Introduction

Most women are diagnosed with breast cancer than any other type of cancer. Breast cancer cases occupy the first position with the highest incidence (44.0) and mortality (15.3) per 100,000 Age-standardized rates (ASR) of world population. The 5-years prevalence (all ages) of breast cancer in Indonesia is high, up to 148.11 per 100,000 population with a death rate of 9.6%. The incidence of new cases of breast cancer in Indonesia is up to 16.6% compared to other cancer cases and has the highest number of new cancer cases in Indonesia.[1] The process of angiogenesis influences the development of breast cancer. Angiogenesis is an essential process for the growth and spread of cancer. In angiogenesis, new blood vessels make it possible for cancer cells to obtain an adequate supply of nutrients and proliferate.[2] Angiogenesis inhibition for breast cancer as a therapeutic approach has shown promising results.[3] This is achieved through inhibition of the vascular endothelial growth factor receptor 2 (VEGFR-2). VEGFR-2 plays a vital role in tumor angiogenesis and is in line with the growth of tumor cells.[3]

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A study involving 98 patients with invasive breast cancer showed a relationship between VEGFR-2 expression and cancer pathology. The results also showed a positive correlation between VEGFR-2 expression and the infiltration of breast cancer in the lymph nodes. Patients with high expression of VEGFR-2 had a poor prognosis.[4]

Other studies have shown that anti-cancer therapy that made VEGFR-2 a therapeutic target had high effectiveness, especially in triple-negative breast cancers.[5] One of the breast cancer therapies with an anti-angiogenesis effect and an inhibitor of VEGFR-2 is sorafenib. Sorafenib is said to be quite effective in increasing the survival rate of patients with invasive and metastatic breast cancer.[6]

Several antioxidants with Sulphur groups are known to provide benefits in inhibiting cancer progression. Antioxidants with Sulphur components that are often used include N-Acetylcysteine (NAC). NAC works in the case of tumors to cause endothelial cell apoptosis and a decrease in microvascular density in the tumor nucleus, resulting in tumor necrosis or apoptosis. NAC works by inducing the production of angiostatin, resulting in the collapse of tumor blood vessels. Studies have shown that the antioxidant NAC has metabolic and antiproliferative effects on breast cancer *in vivo*.[7,8] One of the main active components of Allicin is Sulphur that has antibacterial, antioxidant, and anticarcinogenic effects similiar to NAC.[9] Allicin is obtained from crushed raw garlic. It is formed from the reaction between the enzyme alliinase and a non-protein amino acid material called alliin.[10]

This study aimed to evaluate Allicin from single garlic as an angiogenic potential inhibitor of VEGFR-2 breast cancer through an *in silico* study.

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Materials and Methods

Tool

The tools used in this study were a set of computers with Windows 10 specifications, 64 bits, and ChemDraw Professional 16.0 program, Chem 3D 16.0, and Molegro Virtual Docker 5.

Ligand and receptor preparation

The ligand tested in this study was Allicin, which potency was compared with N-Acetylcysteine (NAC). The structure of Allicin and NAC were obtained from Pubchem.[11] The structure was then redrawn in 2 dimension using ChemDraw Professional 16.0 and converted into a 3-dimensional structure using Chem3D 16.0. The structure obtained was determined by the most stable conformation and the minimum energy. The data were then stored in the form of mol2 {SYBYL2(*.mol2)}. The receptor employed in this study was VEGFR-2. The 3-dimensional structure of VEGFR-2 was obtained from the protein data bank (PDB) with ID code of 4ASD downloaded from Protein Data Bank (PDB).[12] The download results showed that VEGFR-2 bound to the native ligand Sorafenib. The data were then saved in PDB format. By using Molegro Virtual Docker 5, cavity detection was carried out on the receptor. The cavity was where the active native ligand Sorafenib (BAX_1500) utilize as a docking location between the receptor and the test ligand as well as the comparison ligand used in this study.

Molecular docking and compound potential prediction

In this study, Allicin acted as the test ligand, while NAC was the comparison ligand. The docking of Allicin and NAC molecules to the target receptor active site (VEGFR-2) was performed alternately using the Molegro Virtual Docker 5.

The docking process began with detecting the cavity on the target receptor (VEGFR-2). The cavity with a bond between the native ligand (sorafenib) and the receptor (VEGFR-2) was the location of the receptor's active site that would be tested later, using either Allicin or NAC. Docking with the test and comparison ligands was carried out post validation process by re-docking between the receptor and the native ligand. It was declared valid if the re-docking results showed a Root Mean Square Deviation (RMSD) value of less than 2.[13]

After obtaining valid results, docking between Allicin and NAC with the prepared receptors was done alternately. Prediction of anti-angiogenic activity of Allicin and NAC was observed in Rerank score, that is, the energy required for the interaction of the ligand with the receptor indicating the strength of the bond between the ligand and the receptor. The lower score results indicated that the bond was more stable so that lower energy was needed in the bond between the ligand and the receptor, and vice versa.

In the interaction between the ligand and the receptor, the interaction of acid residues was also observed. These bond interactions could be in the form of hydrogen bonds, steric interactions, and electrostatics.

Prediction of Physicochemical and Pharmacokinetic Properties and Toxicity of Compounds (PKCSM)

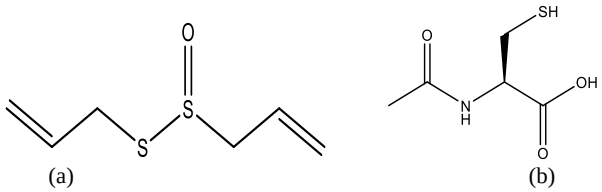
The physicochemical properties of Allicin and NAC were predicted using online pkCSM tool comprising molecular weight (BM), the logarithm of octanol/water partition coefficient (log P), number of rotating bonds between atoms (Torsion), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), and Polar Surface Activity (PSA). In the prediction of the pharmacokinetic properties of compounds consisting of absorption, distribution, metabolism, excretion (ADME), and toxicity tests, online pkCSM tool was also employed. The step began with drawing a 2-dimensional structure of Allicin and NAC compounds using ChemDraw Professional 16.0 program, which was then drawn in a 3-dimensional structure using the Chem3D 16.0 program and saved in the form of a *.sdf file. The structure acquired was translated into a SMILES structure with the help of the Online SMILES Translator.[14] Thereafter, the compounds were processed using online pkCSM tool,[15] for prediction of pharmacokinetic properties and toxicity tests by inputting the compound's SMILES structure into the program.

Results and Discussion

Ligand and Receptor Preparation

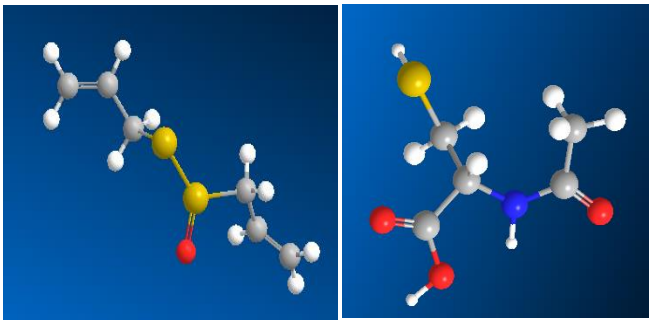
Allicin was the compound tested in this study, and it was compared to N-Acetylcysteine (NAC). Figure 1 shows the results of the 2-dimensional structure using ChemDraw Professional 16.0 for Allicin and NAC. The image conversion of the two compounds was carried out into a 3-dimensional structure using Chem3D 16.0 and conformed to the most stable form and the least energy to optimize the compound structure. The obtained data were stored in the form of mol2 {SYBYL2(* mol2)}. Figure 2 illustrates the results of the optimization of the two compounds.

Vascular endothelial growth factor receptor 2 (VEGFR-2) was one of the receptors that played an essential role in breast cancer angiogenesis. One of the breast cancer therapies that use an anti-angiogenesis approach is Sorafenib.[6] Sorafenib was said to be effective in increasing the survival rate of patients with invasive and metastatic breast cancer, the VEGFR-2 structure chosen in this study was VEGFR-2, forming a complex with Sorafenib in PDB with ID code of 4 ASD. The PDB file was then downloaded and opened using Molegro Virtual Docker. Figure 3 shows the compound-complex between VEGFR-2 complex (4ASD) with native ligand Sorafenib (BAX_1500).



(a) (b)

Figure 1: 2-dimensional structure (a) Allicin; (b) N-Acetylcysteine (NAC)



(a) (b)

Figure 2: 3-dimensional structure with optimization (a) Allicin (b) N-Acetylcysteine

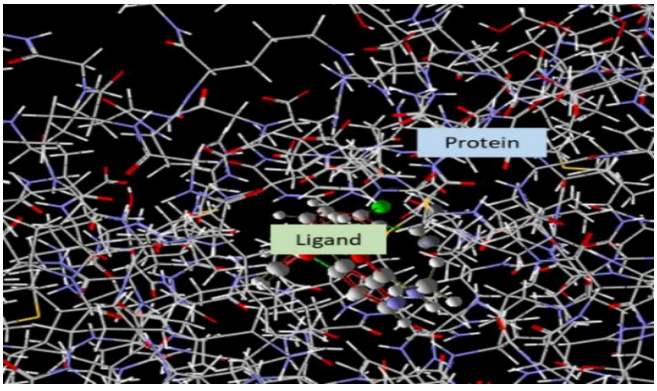


Figure 3: VEGFR-2 complex (4ASD) with native ligand Sorafenib (BAX_1500).

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Molecular Docking and Compound Potential Prediction

The molecular docking process started with the VEGFR-2 receptor input process downloaded from the Protein Data Bank with ID code of 4ASD into the Molegro Virtual Docker program. Then, cavity detection was performed. Some cavities were obtained. However, the bond between the native ligand sorafenib (BAX_1500) and the VEGFR-2 receptor protein was discovered in cavity 2 (see Figure 4).

Before predicting the compound's potential to be tested, it was pivotal to validate the receptor by re-docking between the receptor and the native ligand. Re-docking the VEGFR-2 receptor on the native ligand sorafenib (BAX_1500) obtained RMSD results of 0.868 with a Rerank score of -155.145 kcal/mol. Figure 5a shows the interaction between the receptor (VEGFR-2) and the native ligand sorafenib (BAX_1500). After the validation test was carried out, the receptor with the test and comparison ligands was docked. Figures 5b and 5c depict the interaction between the receptor (VEGFR-2) and the ligand Allicin and NAC.

Several amino acid residues were detected in hydrogen bonding, electrostatic and steric interactions in the interaction between the ligand and the receptor. Table 1 shows the residues formed at the binding between the VEGFR-2 receptor and the ligand Sorafenib (BAX_1500), Allicin, and NAC.

Meanwhile, Table 2 depicts the prediction results of the required binding energy in the interaction of the VEGFR-2 receptor with the ligand.

Figure 6 shows the results of the interaction between the ligands and the VEGFR-2 receptor (PDB with ID code of 4ASD) in cavity 2.

Prediction of physicochemical, pharmacokinetic and toxicity of compounds (pkCSM)

Based on the SMILES structure of each ligand obtained with the assistance of Online SMILES Translator and the results of the input of the SMILES structure into online pkCSM tool, Table 3 and 4 show the results of the predictive physicochemical, pharmacokinetic, and toxicological properties of each compound.

Allicin and NAC are antioxidants with a Sulphur group in their structure (see Figures 1 and 2). *In vivo* administration of NAC had metabolic and antiproliferative effects on breast cancer. Hence, it was suspected that Allicin could act as anticancer through inhibition of the angiogenesis processes in a similar way as NAC.

The VEGFR-2 receptor used in this study was a receptor that form a bond with the native ligand BAX_1500 (sorafenib). From the results of re-docking with native ligands, RMSD results were less than 2 (0.868), indicating that this receptor was valid and could be used for docking with test and comparison ligands.

The results of the prediction of the energy required in the binding process between the ligand and the VEGFR-2 receptor showed that the lowest energy was found in the bond between the receptor and the native ligand BAX_1500 (sorafenib), which was -155.145 Kcal/mol, followed by NAC (-57.5174 Kcal/mol) and Allicin in the third position (-54.2265 Kcal/mol). This indicated that the binding energy required was greatest in the binding between the receptor and Allicin. This implied that the bond between VEGFR-2 and Allicin was less stable than the other ligands. However, the bond energies of Allicin and NAC in VEGFR-2 were not significantly different.

The native ligand BAX_1500 formed the same hydrogen bond, Cys 919, making it possible to increase the antagonistic activity of the compound in the process of breast cancer angiogenesis. However, NAC had more amino acid residues in common with native ligands, namely in hydrogen and steric bonds, which meant that NAC showed more similar activity to native ligands than Allicin.[16]

Lipinski Rule of Five criteria was used in this study to predict the physicochemical properties of the compound. This rule stated that a compound had high permeability properties and was easily absorbed if the compound have a molecular weight of fewer than 500 daltons, Log P < 5, rotational torsion 0-15, hydrogen donor less than 5, hydrogen acceptor less than 10.[17] Based on the results of the predicted physicochemical properties, both Allicin and NAC met the Lipinski Rule of Five criteria, so it could be concluded that both had high permeability and were easily absorbed by the body.

Furthermore, Chander *et al*., (2017) mentioned that absorption through the intestine could affect the performance of drugs given orally. A compound was said to have good intestinal absorption if its absorption ability reached > 80%, and having bad intestinal absorption if its ability was < 30%.[18]

On the other hand, Pires, Blundell, and Ascher (2015) stated that drug have low skin absorption if the log Kp value was > -2.5. In the results of the pharmacokinetic prediction test (see Table 4), it was shown that Allicin had lower skin permeability than NAC, where the log value of Kp Allicin was -1.877 and NAC was -2.735.[19]

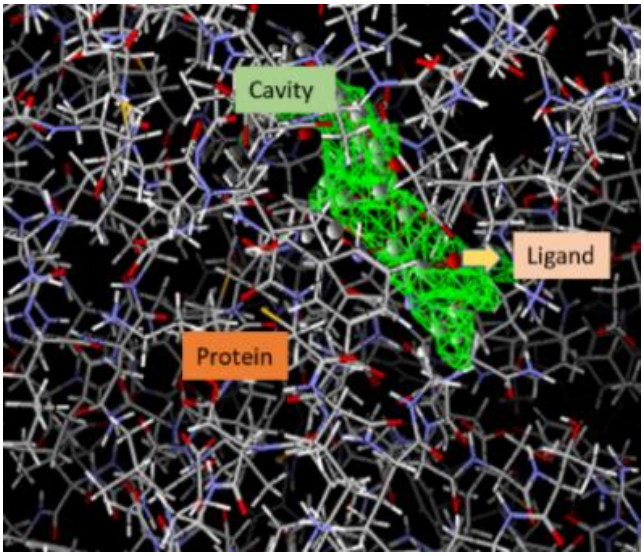
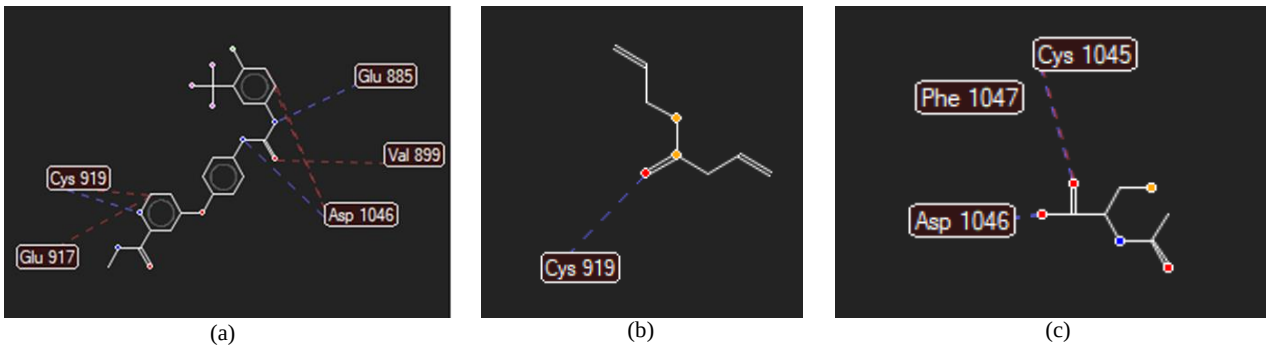


Figure 4: VEGFR-2 complex (4ASD) with native ligand Sorafenib (BAX_1500) in cavity 2



(a) (b) (c)

Figure 5: (a) Interaction of Native Ligand Sorafenib (BAX_1500) with VEGFR-2 receptors (b) Interaction of Allicin with VEGFR-2 receptors (c) Interaction of NAC with VEGFR-2 receptors

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Table 1: Amino Acid Residues involved in the interaction between the Ligand and the VEGFR-2 receptor

Ligand	Hydrogen Bond	Steric Bond	Electrostatic Bond
BAX_1500	Asp1046, Glu885, Cys919	Asp1046, Val899, Cys919, Glu917	-
Allicin	Cys919	-	-
NAC	Cys1045, Asp1046	Cys1045, Asp1046, Phe1047	-

Table 2: Prediction of the binding energy between the receptor and ligand

Ligand	Rerank score
BAX_1500	-155.145
Allicin	-54.2265
NAC	-57.5174

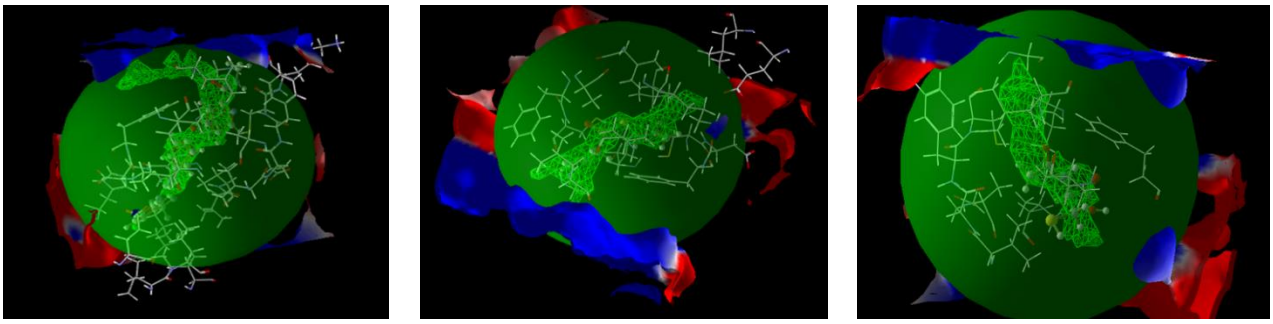
Table 3: Prediction test results of physicochemical properties of Allicin and NAC compounds

Parameter	Allicin	NAC
BM	162.279	163.198
Log P	1.7553	-0.4945
Torsion	5	3
HBA	2	3
HBD	0	3
PSA (A2)	62.082	64.021

BM = Molecular Weight; Log P = logarithm Octanol/water partition coefficient; HBA = hydrogen bond acceptor; HBD = hydrogen bond donor; PSA = Polar Surface Area

Drugs that entered the body needed to be distributed evenly into the blood to enter the tissues. This was expressed in VDss; the higher the value of VDss, the more drugs were distributed into the tissue. According to Pires, Blundell, and Ascher (2015), a compound is said to have a low VDss if the value is < -0.15 and high if the value is > 0.4517. In accordance with Table 4, it was found that Allicin had a better volume of distribution than NAC, where the Allicin VDss was up to -0.045 while that of NAC was -1.355.[19]

The ability of drugs to penetrate the blood-brain barrier is considered as one of the determining factors for the effect of drugs on the central nervous system and the level of drug safety. Pires, Blundell, and Ascher (2015) stated that the drug had a good penetration into the brain if the prediction test results for the BB log is up to > 0.3 and not good if the log weight value reached < -117. Study result showed that Allicin BB log was 0.506 while NAC was -0.355. This meant that both compounds had good penetration properties at the blood-brain barrier, but Allicin had a higher ability than NAC.[19] The process of drug detoxification generally required cytochrome P450 enzymes produced by the liver. The ability of drugs to inhibit this enzyme is expressed in CYP3A4 inhibitors. Meanwhile, the drug's ability to induce cytochrome P450 is expressed in the CYP3A4 substrate. Drugs that could inhibit cytochrome P450 enzymes would decrease drug metabolism and increase drug levels in the blood. On the contrary, if the drug could induce this enzyme, it would increase drug metabolism and decrease drug levels in the blood.[3] Table 4 shows that Allicin was neither a substrate nor an inhibitor of the cytochrome P450 enzyme, so it is relatively safe when given compared to drugs that affected the action of this enzyme.



(a) (b) (c)

Figure 6: Cavity 2 with Ligand (a) BAX_1500 (b) Allicin (c) NAC.

The process of compound elimination could be determined from the total clearance. Total clearance is a combined results of drug metabolism in the liver and excretion in the kidneys.[20] Table 4 shows that the total clearance value of Allicin was greater than that of NAC, where the clearance of Allicin was 0.714 mL/min/kg, while that of NAC was 0.309 mL/min/kg. This means that the elimination of Allicin occurred more slowly when compared to NAC. Organic Cation Transporter (OCT) 2 is a transporter in the kidney that plays a crucial role in the excretion of drugs through the kidneys. OCT2 increase drug uptake from the blood that crosses the basement membrane and reached the proximal renal tubular cells. OCT2 substrate had the potential to cause interactions when given together with OCT2 inhibitor.[21] Based on the results of predictive pharmacokinetic properties, it was found that both Allicin and NAC were not renal OCT2 substrates.The Ames Toxicity Test is used to assess the mutagenicity of a compound, namely the potential for the compound to become a carcinogenic substance.[22] Table 4 shows that Allicin was not mutagenic, while NAC was mutagenic. The results of this study were in accordance with the study conducted by Nikmaturrohana, Lestari, and Lukiati (2020), of which the results showed that both allicin, alliin, and ajoene compounds contained in single garlic did not have mutagenic potential.[23] For the safety of administration to experimental animals, the LD_{50} pharmacokinetic test was carried out. LD_{50} is a certain dose expressed in milligrams of test material per kilogram of test animal body weight, resulting in a 50% death in the test animal population within a certain period.[24] Table 4 shows that LD_{50} for Allicin occurred at 2.366 mol/kg and NAC at a dose of 1.626 mol/kg. Thus, a higher dose of Allicin can be given in experimental animals than NAC.

Table 4: Results of pharmacokinetic (ADME) prediction test and Toxicity of Allicin and NAC

ADME and Toxicity	Allicin	NAC
Intestinal absorption (human) (%)	96.229	77.922
Skin Permeability (log Kp)	-1.877	-2.735
VDss (human (log L/kg)	-0.045	-1.355
Brain Barrier Permeability (log BB)	0.506	-0.355
CYP3A4 Substrate (Yes/No)	No	No
CYP3A4 Inhibitors (Yes/No)	No	No
Total Clearance (log ml/min/kg)	0.714	0.309
Kidney OCT2 Substrate (Yes/No)	No	No
AMES Toxicity (Yes/No)	No	Yes
LD50 (mol/ kg)	2.366	1.626

VDSS = Distribution Volume at Steady State; CYP3A4 = Cytochrome P3A4; Kidney OCT2 substrate = Organic Cation Transporter 2. substrate

Conclusion

In conclusion, Allicin from single garlic has an angiogenic potential as an inhibitor of VEGFR-2 breast cancer through an *in silico* study. Allicin also has an excellent pharmacokinetic profile including intestinal absorption rate, safety level in experimental animals, safety to renal OCT2 and noncarcinogenic as well as having a tolerable toxicity compared to NAC although the energy required is slightly higher. Although it has been proven *in silico*, this study needs to be continued with *in vivo* studies on experimental animals to prove the potential of Allicin in inhibiting the angiogenesis process of breast cancer.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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