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ADMET Analysis of Allicin, Capsaicin, Curcumin, and Genistein Compounds as Cancer Drug Candidates

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ABSTRACT

Background. Cancer treatment with hormone therapy such as Doxorubicin has been widely practised in breast cancer, bowel cancer, and others. However, sometimes the side effects of hormone therapy appear and worsen the patient's condition. The compounds (test compounds) Allicin, Capsaicin, Curcumin and Genistein have potential as anticancer compounds. The similarity of the medicinal properties of the test compounds with Doxorubicin, allows them to be used as cancer drug candidates. In addition, it is necessary to analyse ADMET to determine the efficacy and safety of the test compounds.

Purpose. This study aims to analyse the ADMET of the compounds Allicin, Capsaicin, Curcumin and Genistein.

Method. This research uses the in silico method. Test compounds; Allicin (PubCHem CID 65036), Capsaicin (PubChem CID 1548943), Curcumin (PubChem CID 969516), Genistein (PubChem CID 5280961) and Doxorubicin (PubChem CID 31703) as positive controls were obtained from PubChem. Analysis of test compounds using the PASS online programme to determine the binding activity of compounds with proteins. To determine absorption, distribution, metabolism, excretion, and toxicity (ADMET) using pkCSM online. DruLiTo was used to analyse the physico-chemical properties of the test compounds.

Results. Allicin has good ADMET with Intestinal absorption 96.229 (%absorbed), BBB permeability 0.506 (log BB), Total Clearance 0.704 (log ml/min/kg), and does not cause hepatotoxicity.

Conclusion. It can be concluded that all test compounds have their own advantages and disadvantages, but Allicin has better ADMET than other test compounds. Further research on Molecular Dynamics needs to be done to find out the interaction of test compounds with Caspase-3 Protein.

KEYWORDS

ADMET, Cancer, In Silico

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INTRODUCTION

Cancer is the second most life-threatening disease and one of the top major public health concerns worldwide. In 2018, there were approximately 1.73 million new cases of cancer and more than 609,000 deaths in the United States alone (Siegel, Miller, and Jemal 2018). Despite marked advances in cancer therapy, the reported incidence

of the disease and deaths have not decreased in the past 30 years molecular changes that contribute to cancer development and progression is a key factor in cancer prevention and treatment and cure.

There are several common strategies to target specific cancer cells to inhibit tumour progression and metastasis without causing severe side effects (Umar, Dunn, and Greenwald 2012). Doxorubicin can be used to treat soft tissue and bone sarcomas as well as breast, ovarian, bladder, and thyroid cancers. It is also used to treat acute lymphoblastic leukaemia, acute myeloblastic leukaemia, Hodgkin's lymphoma, and small cell lung cancer (Koleini et al. 2019; M et al. 2019; Marcq et al. 2019; Yu, Chan, and Steingart 2019). However, the drug causes heart problems. The mechanism of action of Doxorubicin-induced cardiac toxicity is different from that of antitumour drugs. It involves increased oxidative stress, downregulation of cardiac-specific genes, and induction of cardiac myocyte apoptosis by Doxorubicin. Doxorubicin acute cardiac toxicity occurs within days of drug administration and occurs in approximately 11% of patients receiving the drug (Johnson-Arbor and Dubey 2024).

The compounds Allicin, Capsaicin, Curcumin, and Genistein have potential as cancer treatments. As a phytochemical antioxidant, Allicin eliminates Reactive Oxigen Species (ROS) and protects cells from oxidative DNA damage (Talib et al. 2024). In addition, Allicin showed inhibition of telomerase activity in both dose and time in gastric cancer cells. Thus, this compound may serve as a potent anticancer agent (Țigu et al. 2021). Capsaicin has been shown to target several proteins involved in the mitochondrial death pathway to initiate apoptosis in different cancer cell lines.

For example, Capsaicin compounds activate cluster of differentiation 95 (CD95) mediated intrinsic and extrinsic apoptotic pathways and suppress the expression of the anti-apoptotic protein, B-cell lymphoma 2 which causes activation of caspase-9 and -3 (Amantini et al. 2009; Kim, Trudel, and Wogan 2009). Curcumin's primary mechanism of action demonstrates its unique anticancer activity including inducing apoptosis and inhibiting tumour proliferation and invasion by suppressing various cellular signalling pathways (Ab et al. 2017). Several studies reported Curcumin's antitumour activity in breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumours (Anand et al. 2008). Genistein inhibits the capacity of cells to penetrate, which is crucial for tumour development and cancer spread (Hou 2022; Huang et al. 2014). In a series of tests, researchers found that genistein stopped progression through the cell cycle and death in cancer cell lines by upregulating p21WAF1 and Bax, as well as suppressing cyclin B1 and Bcl-2 (Alhasan, Aranha, and Sarkar 2001).

Allicin, Capsaicin, Curcumin, Genistein, and Doxorubicin have different anticancer signalling and bind to different proteins. It is necessary to look at the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of each compound or drug.

RESEARCH METHODOLOGY

This study employs an in-silico approach to assess the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties of four natural compounds (Allicin, Capsaicin, Curcumin, and Genistein) and the chemotherapeutic drug Doxorubicin, which are considered for their potential as anticancer agents. ADMET analysis was conducted using online databases and tools, including the pkCSM platform for evaluating the pharmacokinetic properties and the DrugBank database for identifying potential interactions and toxicity profiles. These tools provide a reliable preliminary evaluation of how each compound is likely to behave in the human body, including its bioavailability, distribution in tissues, metabolic pathways, excretion rate, and potential toxicity to critical organs.

For this study, the compounds were selected based on their reported anticancer properties in previous studies. Allicin, Capsaicin, Curcumin, and Genistein were chosen for their known roles as phytochemical antioxidants with anticancer activities, while Doxorubicin was included as a reference drug due to its widespread use and well-documented side effects. The molecular structures of these compounds were retrieved from PubChem and input into the selected ADMET prediction tools. The analysis focused on determining the oral bioavailability, permeability across the blood-brain barrier (BBB), metabolic stability, clearance rates, and potential adverse effects, especially cardiotoxicity for Doxorubicin.

Furthermore, a comparative analysis was conducted to assess the pharmacokinetic and toxicological profiles of the compounds. Parameters such as toxicity to the liver and kidneys, as well as the compound's ability to induce oxidative stress or DNA damage, were specifically examined. The findings from this in-silico analysis were then compared to evaluate which of the compounds, particularly the natural alternatives (Allicin, Capsaicin, Curcumin, and Genistein), could offer comparable or improved safety profiles compared to Doxorubicin. The results aim to provide insights into the feasibility of using these compounds as safer alternatives in cancer treatment regimens, with a focus on minimizing side effects and improving overall therapeutic outcomes.

RESULT AND DISCUSSION

Caspase proteins are one of the targets of cancer treatment. So far, 12 Caspases have been identified in humans with different substrate specificities that cleave next to aspartate residues. Caspases are involved in apoptotic signalling and also in cytokine processing. Caspase-3 is one of the caspases that plays a role in apoptosis. The release of cytochrome c into the cytosol triggers Caspase-3 activation through the formation of an apoptosome complex containing cytochrome c/Apaf-1/caspase-9 (Adrain and Martin 2001; Bratton et al. 2000). The test compounds can be seen in Table 1. In Table 2, Doxorubicin as a positive control proved to have strong potential activity because it has a Pa>Pi value. Meanwhile, Curcumin as a test compound has strong potential activity. The Pa value is the possibility of an active compound in performing biological activity in laboratory experiments, while the Pi value is the opposite (Andhiarto et al. 2023; Chelliah 2008). If a compound has a value of Pa> Pi or Pa>.7, then the compound has the potential to have activity (in this case as an anticancer).

Table 1. Test Compounds Allicin, Allicin, Capsaicin, Curcumin, and Gensitein

Test Compound	Source	Mekanisme	Cancer	References
Allicin	Garlic	Antioxidant, anti-proliferative, and pro-apoptotic	Breast, bladder, lung, colorectal, and prostate	(Özkan et al. 2021)
Capsaicin	Chili peppers	Induces apoptosis and prevents cell growth	Breast, lung, bladder, colon, pancreatic, and colorectal	(Lavorgna et al. 2019)
Curcumin	Turmeric	Induces apoptosis and prevents cell growth	Breast, lung, skin, gastrointestinal, colorectal, and	(Prakobwong et al. 2011)

			prostate	
Genistein	Soybeans	Inhibits angiogenesis and modulates hormone activity	Breast, colorectal, lung, and pancreatic	(Varinska et al. 2015)

Table 2. PASS Prediction Pa and Pi on Caspase-3

Test Compound	Caspase-3	
	Pa	Pi
Allicin	0.299	0.132
Capsaicin	0.457	0.035
Curcumin	0.747	0.009
Genistein	0.459	0.035
Doxorubicin (+)	0.980	0.002

Predictions of physico-chemical properties based on several drug similarity rules can be seen in Table 3. The test compounds Allicin, Curcumin, and Genistein fulfil Lipinski's, Ghost, and Veber's rules. However, the compound Capsaicin did not fulfil Veber's rule. Meanwhile, the positive control Doxorubicin only fulfils Lipinski's rule. Even so, both Capsaicin and Doxorubicin compounds can still penetrate and penetrate the cell membrane (Jadhav, Yadav, and Core 2015).

ADMET predictions can be seen in. Absorption is expressed in intestinal absorption, it can be seen that all test compounds and positive controls have good absorption values above 30%. Distribution is expressed on the VDss value, Doxorubicin has a high VDss which is > 0.45 Log L/Kg and for BBB permeability > 0.3 (Log BB) can penetrate BBB well, if the value is < -1 then it is difficult to penetrate BBB. From these data, Allicin compounds are able to penetrate BBB well. Metabolism is expressed on CYP2D6 substrates and inhibitors, from these data there are no test compounds that act as substrates or inhibitors on CYP2D6, it is possible that all compounds will be metabolised by cytochrome P450 enzymes. Excretion was expressed in total clearance and renal OCT2 substrate values, none of the test compounds affected renal OCT2 substrate and Toxicity was expressed in hepatotoxicity results, Doxorubicin and Capsaicin were hepatotoxic (Pires, Blundell, and Ascher 2015).

Table 3. ADMET Prediction

Senyawa Uji	Intestinal absorption	Skin permeability	VDss	BBB permeability	CYP2D6 substrate	CYP2D6 inhibitor	Total clearence	Renal OCT2 subtrate	Ames toxicity	Hepatotoxicity
Allicin	96.229	-1.877	-0.045	0.506	No	No	0.704	No	No	No

Capsaicin	90.075	-2.825	0.391	-2.41	No	No	1.298	No	No	Yes
Curcumin	82.19	-2.764	-0.215	-0.562	No	No	-0.002	No	No	No
Genistein	93.387	-2.735	0.094	-0.71	No	No	0.151	No	No	No
Doxorunicin (+)	62.372	-2.735	1.647	-1.379	No	No	0.987	No	No	Yes

CONCLUSION

This study critically evaluated the ADMET properties of Allicin, Capsaicin, Curcumin, Genistein, and Doxorubicin to understand their potential as anticancer agents with a focus on safety and efficacy. The in-silico analysis highlighted the favorable pharmacokinetic profiles of the natural compounds, particularly Allicin, which demonstrated good bioavailability, minimal hepatotoxicity, and reasonable distribution across key tissues. While Doxorubicin showed high therapeutic potency, its associated risks, particularly cardiac toxicity, were evident, reinforcing the need for safer alternatives in cancer treatment.

Comparative analysis of the natural compounds revealed that, while they may not yet match Doxorubicin in terms of potency, their lower toxicity profiles and potential for reduced side effects present them as promising candidates for further research and development. Allicin, Capsaicin, Curcumin, and Genistein all exhibited unique mechanisms of action, targeting different proteins involved in cancer cell growth and apoptosis. These findings underscore the importance of integrating natural compounds with conventional therapies to improve patient safety and treatment outcomes.

The results of this study suggest that future empirical research, particularly in vivo and clinical trials, is necessary to validate the findings from this in-silico analysis. Moreover, further optimization of these natural compounds, coupled with a deeper understanding of their molecular mechanisms, could lead to the development of more effective and less toxic cancer therapies. These efforts would be crucial for advancing personalized, precision medicine in oncology.

AUTHORS' CONTRIBUTION

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.
Author 2: Conceptualization; Data curation; In-vestigation.
Author 3: Data curation; Investigation.

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