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Potential anticancer agents identification of *Hystrix brachyura* bezoar through gas chromatography-mass spectrometry-based metabolomics and protein-ligand interaction with molecular docking analyses

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Abstract

Background: Bezoar (PB) is a rare, solidified form of undigested food commonly found in the gastrointestinal tract of porcupine (*Hystrix brachyura*). It is believed to be traditionally used to treat various diseases including different kinds of cancers in Malaysia. However, its active principles have not been found out yet. The purpose of this study was to investigate the anticancer property of PB extract as well as to identify the metabolites responsible for its anticancer effect through a widely acclaimed metabolomics approach. **Methods:** Initially, 25 PB extracts using various solvent ratios of methanol–water (100, 75, 50, 25, 0% v/v) were prepared in regard to metabolomics approach and subsequently the cytotoxicity of each extract was determined against (melanoma) A375 cell line. The metabolites profiling of the most potent extract was conducted using gas chromatography mass spectrometry (GC–MS) and in silico investigation was performed on Bcl-2 and cyclin/CDK1 complex protein. **Results:** The correlation of the bioactivity with GC–MS data produced an orthogonal partial least square (OPLS) model which pinpointed four putative active compounds namely (1) cholest-7-en-3-beta-ol,4,4-dimethyl-,acetate; (2) 4-androsten-4-ol-3,17-dione; (3) isolongifolol and (4) gallic acid. The in silico data suggested the binding score and binding mode of active metabolites with the amino acid residues of protein via hydrophobic interactions. **Conclusion:** This study is the first to report the identified anticancer compounds from PB extract and evaluate them using molecular docking. This further confirms and justifies its traditional usage as an alternative medicine for the treatment of cancer in Malaysia. © 2023 The Author(s)

Author Keywords

Bcl-2; Cyclin B/CDK1; GC–MS; *Hystrix brachyura*; Metabolomics; Molecular docking

References

- Abarca-Vargas, R., Peña Malacara, C., Petricevich, V.
Characterization of Chemical Compounds with Antioxidant and Cytotoxic Activities in *Bougainvillea x buttiana* Holttum and Standl, (var. Rose) Extracts
(2016) *Antioxidants*, 5 (4), p. 45.
- Aborehab, N.M., Osama, N.
Effect of Gallic acid in potentiating chemotherapeutic effect of Paclitaxel in HeLa cervical cancer cells
(2019) *Cancer Cell Int.*, 19 (1), pp. 1-13.
- Ali Khan, A., Alanazi, A.M., Jabeen, M., Chauhan, A., Abdelhameed, A.S.
Design, Synthesis and In Vitro Anticancer Evaluation of a Stearic Acid-based Ester Conjugate
(2013) *Anticancer Res*, 33, pp. 2517-2524.

- Antony, P., Vijayan, R.
Acetogenins from *Annona muricata* as potential inhibitors of antiapoptotic proteins: A molecular modeling study
(2016) *Drug Des. Devel. Ther.*, 10, pp. 1399-1410.
- Azliza, M.A., Ong, H.C., Vikineswary, S., Noorlidah, A., Haron, N.W.
Ethno-medicinal resources used by the Temuan in Ulu Kuang village
(2012) *Studies on Ethno-Medicine*, 6 (1), pp. 17-22.
- Azman, S., Zulkepli, N.A.
Abdul Wahab, R. 2014. Novel apoptotic regulators in carcinogenesis. In: Novel Apoptotic Regulators in Carcinogenesis. Springer Science+Business Media Dordrecht 2012. Doi: 10.1007/978-94-007-4917-7.
- Barroso, M.D.S.
The Bezoar Stone: A Princely Antidote, The Távora Sequeira Pinto Collection – Oporto
(2014) *Acta Med. Hist. Adriat.*, 12 (1), pp. 77-98.
- Barroso, S.
Chapter 11. Animal Stones and the Dark Age of Bezoars
(2017) *Toxicology in the Middle Ages and Renaissance*, pp. 115-123.
Elsevier
- Brylinski, M.
Aromatic interactions at the ligand–protein interface: Implications for the development of docking scoring functions
(2018) *Chem. Biol. Drug Des.*, 91 (2), pp. 380-390.
- Chen, J., Ding, J., Wang, Z., Zhu, J., Wang, X., Du, J.
Identification of downstream metastasis-associated target genes regulated by LSD1 in colon cancer cells
(2017) *Oncotarget*, 8 (12), pp. 19609-19630.
- Chow, J.P.H., Poon, R.Y.C., Ma, H.T.
Inhibitory Phosphorylation of Cyclin-Dependent Kinase 1 as a Compensatory Mechanism for Mitosis Exit
(2011) *Mol. Cell. Biol.*, 31 (7), pp. 1478-1491.
- Correia, C., Lee, S.-H., Meng, X.W.
Vincelettee, Nicole.D, Knorr, Katherine. L. B., Ding, H., Nowakowski, Grzegorz. S., & Dai, Haiming, Kaufmann, Scott. H. 2015. Emerging understanding of Bcl-2 biology: Implications for neoplastic progression and treatment. *Biochemistry Biophysical Acta*, 1853(7), 1658–1671. Doi: 10.1016/j.physbeh.2017.03.040.
- Diaz-Aragon, R., Ramirez-Ricardo, J., Cortes-Reynosa, P., Simoni-Nieves, A., Gomez-Quiroz, L.-E., Perez Salazar, E.
Role of phospholipase D in migration and invasion induced by linoleic acid in breast cancer cells
(2019) *Mol Cell Biochem*, 457 (1-2), pp. 119-132.
- Duffin, C.J.
Porcupine stones
(2013) *Pharm. Hist.*, 43 (1), pp. 13-22.
- Firus Khan, A.Y., Ahmed, Q.U., Narayanamurthy, V., Razali, S., Asuhaimi, F.A., Saleh, M.S.M., Johan, M.F., Wahab, R.A.
Anticancer activity of grassy *Hystrix brachyura* bezoar and its mechanisms of action: An in vitro and in vivo based study
(2019) *Biomedicine and Pharmacotherapy*, 114.

- Firus Khan, A.Y., Asuhaimi, F.A., Jalal, T.K., Roheem, F.O., Natto, H.A., Johan, M.F., Ahmed, Q.U., Wahab, R.A.
Hystrix brachyura bezoar characterization, antioxidant activity screening, and anticancer activity on melanoma cells (A375): A preliminary study
(2019) *Antioxidants*, 8 (2).
- Fokunang, C.N., Ndikum, V., Tabi, O.Y., Jiofack, R.B., Ngameni, B., Guedje, N.M., Tembe-Fokunang, E.A., Lohoue, J.
Traditional medicine: Past, present and future research and development prospects and integration in the national health system of Cameroon
(2011) *Afr. J. Tradit. Complement. Altern. Med.*, 8 (3).
- Hata, A.N., Engelman, J.A., Faber, A.C.
The BCL2 family: Key mediators of the apoptotic response to targeted anticancer therapeutics
(2015) *Cancer Discov.*, 5 (5), pp. 475-487.
- Hill, J., Mills, C., Li, Q., Smith, J.S.
Prevalence of traditional, complementary, and alternative medicine use by cancer patients in low income and lower-middle income countries
(2019) *Glob. Public Health*, 14 (3), pp. 418-430.
- Kale, J., Osterlund, E.J., Andrews, D.W.
BCL-2 family proteins: Changing partners in the dance towards death
(2018) *Cell Death Differ.*, 25 (1), pp. 65-80.
- Lim, N.T., Wang, D.
Records of the Malayan porcupine, *Hystrix brachyura* (Mammalia: Rodentia: Hystricidae) in Singapore
(2016) *Nature in Singapore*, 9 (August), pp. 63-68.
- Lindqvist, A., Van Zon, W., Rosenthal, C.K., Wolthuis, R.M.F.
Cyclin B1-Cdk1 activation continues after centrosome separation to control mitotic progression
(2007) *PLoS Biol.*, 5 (5), pp. 1127-1137.
- Lunde, D., Aplin, K., Molur, S.
***Hystrix brachyura*, Malayan Porcupine. In International Union for Conservation of**
(2008) *Nature*, Vol. T10749A321.
- Manier, S.K., Keller, A., Schäper, J., Meyer, M.R.
Untargeted metabolomics by high resolution mass spectrometry coupled to normal and reversed phase liquid chromatography as a tool to study the in vitro biotransformation of new psychoactive substances
(2019) *Sci. Rep.*, 9 (1), pp. 1-11.
- Montero, J., Letai, A.
Why do BCL-2 inhibitors work and where should we use them in the clinic?
(2018) *Cell Death Differ.*, 25 (1), pp. 56-64.
- Murugesu, S., Ibrahim, Z., Ahmed, Q., Yusoff, N.N., Uzir, B., Perumal, V., Abas, F., Saari, K.
***Clinacanthus nutans* Lindau Leaves by Gas Metabolomics and Molecular Docking Simulation**
(2018) *Molecules*, 23 (2402), pp. 1-21.
- Pacheco, B.S., dos Santos, M.A.Z., Schultze, E., Martins, R.M., Lund, R.G., Seixas, F.K., Colepicolo, P., De Pereira, C.M.P.
Cytotoxic activity of fatty acids from Antarctic macroalgae on the growth of human

breast cancer cells

(2018) *Front. Bioeng. Biotechnol.*, 6 (DEC), pp. 1-10.

- Petros, A.M., Olejniczak, E.T., Fesik, S.W.
Structural biology of the Bcl-2 family of proteins
(2004) *Biochimica et Biophysica Acta - Molecular Cell Research*, 1644 (2-3), pp. 83-94.
- Porter, J., Payne, A., de Candole, B., Ford, D., Hutchinson, B., Trevitt, G., Turner, J., Stubberfield, C.
Tetrahydroisoquinoline amide substituted phenyl pyrazoles as selective Bcl-2 inhibitors
(2009) *Bioorg. Med. Chem. Lett.*, 19 (1), pp. 230-233.
- Potapova, T., Daum, J.R., Byrd, K.S., Gorbsky, G.J.
Fine Tuning the Cell Cycle: Activation of the Cdk1 Inhibitory Phosphorylation Pathway during Mitotic Exit
(2009) *Mol. Biol. Cell*, 20, pp. 1737-1748.
- Pyrkov, T.V., Ozerov, I.V., Blitskaia, E.D., Efremov, R.G.
Molecular docking: role of intermolecular contacts in formation of complexes of proteins with nucleotides and peptides
(2010) *Bioorg. Khim.*, 36 (4), pp. 482-492.
- Raj, H., Poelarends, G.J.
The roles of active site residues in the catalytic mechanism of methylaspartate ammonia-lyase
(2013) *FEBS Open Bio*, 3, pp. 285-290.
- Ren, J.G., Seth, P., Ye, H., Guo, K., Hanai, J.I., Husain, Z., Sukhatme, V.P.
Citrate Suppresses Tumor Growth in Multiple Models through Inhibition of Glycolysis, the Tricarboxylic Acid Cycle and the IGF-1R Pathway
(2017) *Sci. Rep.*, 7 (1), pp. 1-13.
- Saleh, M.S.M., Siddiqui, M.J., Zaiton, S., So, M.
Correlation of FT-IR Fingerprint and α -Glucosidase Inhibitory Activity of Salak (Salacca zalacca) Fruit Extracts Utilizing Orthogonal Partial Least Square
(2018), Doi: 10.3390/molecules23061434.
- Sathishkumar, N., Sathiyamoorthy, S., Ramya, M., Yang, D., Lee, H.N., Yang, D.
Molecular docking studies of anti-apoptotic BCL-2, BCL-XL, and MCL-1 proteins with ginsenosides from Panax ginseng
(2012) *J. Enzyme Inhib. Med. Chem.*, 27 (5), pp. 685-692.
- Shamsi, Z., Shukla, D.
How does evolution design functional free energy landscapes of proteins? A case study on the emergence of regulation in the Cyclin Dependent Kinase family
(2020) *Mol. Syst. Des. Eng.*, 5 (1), pp. 392-400.
- Sun, G., Zhang, S., Xie, Y., Zhang, Z., Zhao, W.
Gallic acid as a selective anticancer agent that induces apoptosis in SMMC-7721 human hepatocellular carcinoma cells
(2016) *Oncol. Lett.*, 11 (1), pp. 150-158.
- Wood, D.J., Endicott, J.A.
Structural insights into the functional diversity of the CDK–cyclin family
(2018) *Open Biol.*, 8 (9).
- Xu, K., Liang, X., Wang, F., Xie, L., Xu, Y., Liu, J., Qian, X.
Induction of G2/M phase arrest and apoptosis by potent antitumor APCA in human cervix carcinoma cells
(2011) *Anticancer Drugs*, 22 (9), pp. 875-885.

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