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Development of chemometric-assisted supercritical fluid extraction of effective and natural tyrosinase inhibitor from Syzygium aqueum leaves

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Abstract

Tyrosinase is a key enzyme in enzymatic browning, causing quality losses in food through the oxidation process. Thus, the discovery of an effective and natural tyrosinase inhibitor via green technology is of great interest to the global food market due to food security and climate change issues. In this study, Syzygium aqueum (S. aqueum) leaves, which are known to be rich in phenolic compounds (PC), were chosen as a natural source of tyrosinase inhibitor, and the effect of the sustainable, supercritical fluid extraction (SFE) process was evaluated. Response surface methodology-assisted supercritical fluid extraction (RSM-assisted SFE) was utilized to optimize the PCs extracted from S. aqueum. The highest amount of PC was obtained at the optimum conditions (55 °C, 3350 psi, and 70 min). The IC50 (661.815 μg/mL) of the optimized extract was evaluated, and its antioxidant activity (96.8 %) was determined. Gas chromatography-mass spectrometry (GC–MS) results reveal that 2′,6′-dihydroxy-4′-methoxychalcone (2,6-D4MC) (82.65 %) was the major PC in S. aqueum. Chemometric analysis indicated that 2,6-D4MC has similar chemical properties to the tyrosinase inhibitor control (kaempferol). The toxicity and physiochemical properties of the novel 2,6-D4MC from S. aqueum revealed that the 2,6-D4MC is safer than kaempferol as predicted via absorption, distribution, metabolism, and excretion (ADME) evaluation. Enzyme kinetic analysis shows that the type of inhibition of the optimized extract is non-competitive inhibition with Km = 1.55 mM and Vmax = 0.017 μM/s. High-performance liquid chromatography (HPLC) analysis shows the effectiveness of S. aqueum as a tyrosinase inhibitor. The mechanistic insight of the tyrosinase inhibition using 2,6-D4MC was successfully calculated using density functional theory (DFT) and molecular docking approaches. The findings could have a significant impact on food security development by devising a sustainable and effective tyrosinase inhibitor from waste by-products that is aligned with the United Nation's SDG 2, zero hunger. © 2024 Elsevier B.V.

Author Keywords

Chemometric; Density functional theory; Response surface methodology; Syzygium aqueum; Tyrosinase inhibitor

Index Keywords

Climate change, Density functional theory, Effluent treatment, Flavonoids, Gas chromatography, High performance liquid chromatography, Supercritical fluid extraction, Supercritical fluids, Surface properties; Chemometrices, Density-functional-theory, Enzymatic browning, Food security, Kaempferol, Key enzymes, Phenolic compounds, Response-surface methodology, Syzygium aqueum, Tyrosinase inhibitors; Mass spectrometry

References

- Micheloni, O.B., Farroni, A.E., García, P., Furlan, R.L.E.
  Rapid autographic method for detection of enzymatic browning inhibitors based on enzyme immobilization
  (2018) *Food Chem.*, 269, pp. 638-643.
- Moon, K.M., Kim, C.Y., Yeul Ma, J., Lee, B.
  Xanthone-related compounds as an anti-browning and antioxidant food additive
  (2019) *Food Chem.*, 274, pp. 345-350.

- Likhitwitayawuid, K.
  Stilbenes with Tyrosinase inhibitory activity
  (2014) *Curr. Sci.*, 94 (1), pp. 44-52.

- Kumar, M., Dahuja, A., Tiwari, S., Punia, S., Tak, Y., Amarowicz, R., Bhoite, A.G., Kaur, C.
  Recent trends in extraction of plant bioactives using green technologies: a review
  (2021) *Food Chem.*, 353.

- Manaharan, T., Chakravarthi, S., Radhakrishnan, A.K., Palanisamy, U.D.
  In vivo toxicity evaluation of a standardized extract of Syzygium aqueum leaf
  (2014) *Toxicol. Rep.*, 1, pp. 718-725.

- Sobeh, M., Mahmoud, M.F., Petruk, G., Rezq, S., Ashour, M.L., Youssef, F.S., El-Shazly, A.M., Wink, M.
  Syzygium aqueum: A polyphenol-rich leaf extract exhibits antioxidant, hepatoprotective, pain-killing and anti-inflammatory activities in animal models
  (2018) *Front. Pharmacol.*, 9, p. 566.

- Hasanov, J., Salikhov, S., Oshchepkova, Y.
  Techno-economic evaluation of supercritical fluid extraction of flaxseed oil
  (2023) *J. Supercrit. Fluids*, 194.

- Soh, S.H., Jain, A., Lee, L.Y., Chin, S.K., Yin, C.Y., Jayaraman, S.
  Techno-economic and profitability analysis of extraction of patchouli oil using supercritical carbon dioxide
  (2021) *J. Clean. Prod.*, 297.

- Azwanida, N.N.
  A review on the extraction methods use in medicinal plants, principle, strength and limitation
  (2015) *Med. Aromat. Plants*, 4 (3), pp. 1-6.

- Zhang, Q.-W., Lin, L.-G., Ye, W.-C.
  Techniques for extraction and isolation of natural products: a comprehensive review
  (2018) *Chin. Med.*, 13, pp. 20-21.

- Pereira, P., Mauricio, E.M., Duarte, M.P., Lima, K., Fernandes, A.S., Bernardo-Gil, G., Cebola, M.J.
  Potential of supercritical fluid myrtle extracts as an active ingredient and co-preservative for cosmetic and topical pharmaceutical applications
  (2022) *Sustain. Chem. Pharm.*, 28.

- Milovanovic, S., Grzegorczyk, A., Swiątek, Ł., Dębczak, A., Tyskiewicz, K., Konkol, M.
  Dandelion seeds as a new and valuable source of bioactive extracts obtained using the supercritical fluid extraction technique
  (2022) *Sustain. Chem. Pharm.*, 29.

- Ahmad, M.N., Karim, N.U., Normaya, E., Mat Piah, N., Iqbal, A., Ku Bulat, K.H.
  Artocarpus altilis extracts as a food-borne pathogen and oxidation inhibitors: RSM, COSMO RS, and molecular docking approaches
  (2020) *Sci. Rep.*, 10, p. 19573.

- Zhang, Q.W., Lin, L.G., Ye, W.C.
  Techniques for extraction and isolation of natural products: a comprehensive review
  (2018) *Chin. Med.*, 13, p. 20.

- Frohlich, P.C., Santos, K.A., Palú, F., Cardozo-Filho, L., da Silva, C., da Silva, E.A.
  Evaluation of the effects of temperature and pressure on the extraction of eugenol

from clove (Syzygium aromaticum) leaves using supercritical CO₂
J. Supercrit. Fluids, 143, pp. 313-320.

- Ahmad, M.N., Azli, N.H.M., Ismail, H., Iqbal, M.A., Piah, B.M., Normaya, E.
Inhibitory effects of Manihot Esculenta extracts on food-borne pathogens and their antioxidants properties: supercritical fluid extraction, statistical analysis, and molecular docking study
(2020) *J. Food Process Eng.*, 43 (9).

- Sun, C., Wu, Z., Wang, Z., Zhang, H.
Effect of ethanol/water solvents on phenolic profiles and antioxidant properties of Beijing propolis extracts
(2015) *Evid. Based Complementary Altern. Med.*, p. 1-9. 62.

- Bendif, H., Adouni, K., Miara, M.D., Baranauskiene, R., Kraujalise, P., Venskutonise, P.R., Nabavif, S.M., Maggi, F.
Essential oils (EOs), pressurized liquid extracts (PLE) and carbon dioxide supercritical fluid extracts (SFE-CO₂) from Algerian Thymus munbyanus as valuable sources of antioxidants to be used on an industrial level
(2018) *Food Chem.*, 260, pp. 289-298.

- Ashraf, Z., Rafiq, Z., Seo, Z., Babar, M.M., Zaidi, N.S.
Synthesis, kinetic mechanism and docking studies of vanillin derivatives as inhibitors of mushroom tyrosinase
(2015) *Bioorg. Med. Chem.*, 23 (17), pp. 5870-5880.

- Zolghadri, S., Bahrami, A., Khan, M.T.H., Munoz-Munoz, J., Garcia-Molina, F., Garcia-Canovas, F., Saboury, A.A.
A comprehensive review on tyrosinase inhibitors
(2019) *J. Enzyme Inhib. Med. Chem.*, 34, pp. 279-309.

- Shamsuri, S.S., Normaya, E., Ismail, H., Iqbal, A., Mat Piah, M.B., Farina, Y., Hamzah, A.S., Ahmad, M.N.
(1E)-1-(2-Pyrazinyl)ethanone thiosemicarbazone (PT) as a tyrosinase inhibitor with anti- browning activity: spectroscopy, DFT and molecular docking studies
(2023) *J. Mol. Struct.*, 1291.

- Zhang, L., Zhao, X., Tao, G.J., Chen, J., Zheng, Z.P.
Investigating the inhibitory activity and mechanism differences between norartocarpetin and luteolin for tyrosinase: a combinatory kinetic study and computational simulation analysis
(2017) *Food Chem.*, 223, pp. 40-48.

- Normaya, E., Fazli, M., Norazmi Ahmad, M., Ku Bulat, K.H.
COSMO-RS and DFT studies on development and optimization of quercetin as a chemosensor for Fe³⁺ recognition in aqueous medium
(2019) *J. Mol. Struct.*, 1184, pp. 538-545.

- Hassanuddin, N.A., Normaya, E., Ismail, H., Iqbal, A., Mat Piah, M.B., Hamid, S.A., Ahmad, M.N.
Methyl 4-Pyridyl ketone thiosemicarbazone (4-PT) as an effective and safe inhibitor of mushroom tyrosinase and antibrowning agent
(2024) *Int. J. Biol. Macromol.*, 255.

- Rodionova, O.Y., Pomerantsev, A.L.
Chemometric tools for food fraud detection: the role of target class in non-targeted analysis
(2020) *Food Chem.*, 317.

- Keith, J.A., Vassilev-Galindo, V., Cheng, B., Chmiela, S., Gastegger, M., Klaus-Robert, M., Tkatchenko, A.

Combining machine learning and computational chemistry for predictive insights into chemical systems
(2021) *Chem. Rev.*, 121 (16), pp. 9816-9872.

- Ranbir, M., Kumar, G., Singh, J., Singh, N., Kaur, N., Singh, N.
Machine learning-based analytical systems: food forensics
(2022) *ACS Omega*, 7, pp. 47518-47535.

- Granata, D., Santos, J.S., Escher, G.B., Ferreira, B.L., Maggio, R.M.
Use of principal component analysis (PCA) and hierarchical cluster analysis (HCA) for multivariate association between bioactive compounds and functional properties in foods: a critical perspective
(2018) *Trends Food Sci. Technol.*, 72, pp. 83-90.

- Cornejo-Báez, A.X., Peña-Rodríguez, L.M., Alvarez-Zapata, R., Vazquez-Hernández, M., Sánchez-Medina, A.
Chemometrics: a complementary tool to guide the isolation of pharmacologically active natural products
(2020) *Drug Discov. Today*, 25, pp. 27-37.

- Normaya, E., Syuhada, R., Ismail, H., Ahmad, M., Yarmo, M., Bulat, K.H.K.
Chemosensor development of Cu²⁺ recognition using 1,5-diphenylthiocarbazone: optimization, COSMO-RS and DFT studies
(2019) *J. Braz. Chem. Soc.*, 30 (9), pp. 1850-1859.

- Ahmad, M.N., Liew, S.L., Yarmo, M.A., Said, M.
Optimization of protease extraction from horse mango (Mangifera foetida Lour) kernels by a response surface methodology
(2012) *Biosci. Biotechnol. Biochem.*, 8 (2012), pp. 1438-1444.

- Jha, Sit
Comparison of response surface methodology (RSM) and artificial neural network (ANN) modelling for supercritical fluid extraction of phytochemicals from Terminalia chebula pulp and optimization using RSM coupled with desirability function (DF) and genetic algorithm (GA) and ANN with GA
(2021) *Ind. Crop. Prod.*, 170.

- Khaw, K.Y., Parat, M.O., Shaw, P.N., Falconer, J.R.
Solvent supercritical fluid technologies to extract bioactive compounds from natural sources: A review
(2017) *Molecules*, 22 (7), pp. 7-15.

- Yim, S.Y., Chan, Y.H., Yusup, S., Johri, K., Quitain, A.T., Dailin, D.J.
Supercritical extraction of value-added compounds from empty fruit bunch: An optimization study by response surface methodology
(2019) *Advances in Feedstock Conversion Technologies for Alternative Fuels and Bioproducts New Technologies, Challenges and Opportunities*, pp. 281-298.
M. Hosseini 1st Eds Woodhead Publishing United Kingdom

- Spence, A.J., Jimenez-Flores, R., Qian, M., Goddik, L.
The influence of temperature and pressure factors in supercritical fluid extraction for optimizing nonpolar lipid extraction from buttermilk powder
(2009) *J. Dairy Sci.*, 92 (2), pp. 458-468.

- Wang, L., Yang, B., Du, X., Yi, C.
Optimisation of supercritical fluid extraction of flavanoids from Pueraria lobata
(2008) *Food Chem.*, 108 (2), pp. 737-741.

- Thapa, P., Choi, D.H., Kim, M.S., Jeong, S.H.
Effects of granulation process variables on the physical properties of dosage forms

by combination of experimental design and principal component analysis
(2018) *Asian J. Pharm. Sci.*, 17 (48), pp. 5-16.

- El-Nashar, H.A.S., El-Din, M.I.G., Hritcu, L., Eldahsan, O.A.
Insights on the inhibitory power of flavonoid on tyrosinase activity: a survey from 2016 to 2021
(2021) *Molecules*, 26 (24), p. 7546.

- Taherkhani, N., Gheibi, N.
Inhibitory effects of quercetin and kaempferol as two propolis derived flavonoids on tyrosinase enzyme
(2014) *Biotechnol. Healthc.*, 1 (2), p. e22242.

- Biswas, R., Chanda, J., Kar, A., Mukherjee, P.K.
Tyrosinase inhibitory mechanism of betulinic acid from Dillenia indica
(2017) *Food Chem.*, 232, pp. 689-696.

- Kang, S.M., Heo, S.J., Kim, K.N., Lee, S.H., Yang, H.M., Kim, A.D., Jeon, Y.J.
Molecular docking studies of a phlorotannin, dieckol isolated from Ecklonia cava with tyrosinase inhibitory activity
(2012) *Bioorg. Med. Chem.*, 20, pp. 311-316.

- Yoon, J.H., Shim, J.S., Cho, Y., Baek, N.I., Lee, C.W., Kim, H.S., Hwang, J.K.
Depigmentation of melanocytes by isopanduratin A and 4-hydroxypanduratin A isolated from Kaempferia pandurata Roxb
(2007) *Biol. Pharm. Bull.*, 30 (11), pp. 2141-2145.

- Kim, B.H., Park, K.C., Park, J.H., Lee, C.G., Ye, S.K., Park, J.Y.
Inhibition of tyrosinase activity and melanin production by the chalcone derivative 1-(2-cyclohexylmethoxy-6-hydroxy-phenyl)-3-(4-hydroxymethyl-phenyl)-propenone
(2016) *Biochem. Biophys. Res. Commun.*, 489 (4), pp. 648-654.

- Kim, J.Y., Kim, J.Y., Jenis, J., Li, Z.P., Ban, Y.J., Baiseitova, A., Park, K.H.
Tyrosinase inhibitory study of flavonolignans from the seeds of Silybum marianum (Milk thistle)
(2019) *Bioorg. Med. Chem.*, 27 (2), pp. 2499-2507.

- Kim, J.H., Jang, D.H., Lee, K.W., Kim, K.D., Shah, A.B., Zhumanova, K., Park, K.H.
Tyrosinase inhibition and kinetic details of puerol a having but-2-enolide structure from Amorpha fruticose
(2020) *Molecules*, 25, p. 2344.

- Hassan, S., Adam, F., Abu Bakar, M.R., Abdul Mudalip, S.K.
Evaluation of solvents effect on solubility, intermolecular interaction energies and habit of ascorbic acid crystals
(2019) *J. Saudi Chem. Soc.*, 23 (2), pp. 239-248.

- Schroeder, K., Bremm, K.D., Alépée, N., Bessems, J.G.M., Blaauboer, B., Boehn, S.N., Burek, C., Diembeck, W.
Report from the EPAA workshop: in vitro ADME in safety testing used by EPAA industry sectors
(2011) *Toxicol. In Vitro*, 25, pp. 589-604.

- Borges, E.M., Gelinski, J.I.L.N., Souza, V.C.D.O., Batista, F.B., Jr, B.L.
Monitoring the authenticity of organic rice via chemometric analysis of elemental data
(2015) *Int. Food Res. J.*, 77 (3), pp. 299-309.

- Paul, A., Harrington, P.D.B.
Chemometric applications in metabolomic studies using chromatography-mass

spectrometry
(2021) *TrAC Trends Anal. Chem.*, 135.

- Mary, Y.S., Yohannan, P.C., Sapnakumari, M., Narayana, B., Sarojini, B.K., Al-Saadi, A.A., Van, A.C., War, J.A.
Molecular structure, FT-IR, vibrational assignments, HOMO-LUMO, MEP, NBO analysis and molecular docking study of ethyl-6-(4-chlorophenyl)-4-(4-fluorophenyl)-2-oxocyclohex-3-ene-1-carboxylate
(2015) *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, 138, pp. 73-84.

- Larik, F.A., Saeed, A., Channar, P.A., Muqadar, U., Abbas, Q., Hassan, M., Seo, S.Y., Bolte, M.
Design, synthesis, kinetic mechanism and molecular docking studies of novel 1-pentanoyl-3-arylthioureas as inhibitors of mushroom tyrosinase and free radical scavengers
(2017) *Eur. J. Med. Chem.*, 141, pp. 273-281.

- Tehrani, M.B., Emani, P., Rezaei, Z., Khoshneviszadeh, M., Ebrahimi, M., Edraki, N., Mahdavi, M., Khoshneviszadeh, M.
Phthalimide-1,2,3-triazole hybrid compounds as tyrosinase inhibitors; synthesis, biological evaluation and molecular docking analysis
(2019) *J. Mol. Struct.*, 1176, pp. 86-93.

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