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Assessment of antiemetic activity of dihydrocoumarin: *In vivo* and *in silico* approaches on receptor binding affinity and modulatory effects

Md. Abu Saim [a,1], Md. Shimul Bhuia [a,b,1,*], Tanzila Akter Eity [a,c], Raihan Chowdhury [a,b], Nowreen Tabassum Ahammed [a,e], Siddique Akber Ansari [d], Kazi Nadim Hossain [a,b], Afroza Akter Luna [a,b], Md. Hanif Munshi [a,f], Muhammad Torequl Islam [a,b,g,*]

[a] *Bioinformatics and Drug Innovation Laboratory, BioLuster Research Center Ltd., Gopalganj 8100, Dhaka, Bangladesh*
[b] *Department of Pharmacy, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh*
[c] *Department of Biotechnology and Genetic Engineering, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh*
[d] *Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia*
[e] *Department of Biology, Touro University, New York City, NY, United States*
[f] *Department of Textile Engineering, Uttara University, Dhaka, Bangladesh*
[g] *Pharmacy Discipline, Khulna University, Khulna 9208, Bangladesh*

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ABSTRACT

Dihydrocoumarin (DCN) is a natural compound widely used in the flavor industry and has antioxidant and anti-inflammatory properties. However, its potential antiemetic effects on gastrointestinal disturbances remain untested. This study emphasizes assessing the antiemetic properties of the natural aromatic compound DCN using copper sulfate ($CuSO_4.5H_2O$)-induced emetic model on chicks, and an *in silico* approach was also adopted to estimate the possible underlying mechanisms. Two doses (25 and 50 mg/kg b.w.) of DCN and several referral drugs considered positive controls (PCs), including domperidone (6 mg/kg), hyoscine (21 mg/kg), aprepitant (16 mg/kg), diphenhydramine (10 mg/kg), and ondansetron (5 mg/kg), were orally administered to chicks. The vehicle was provided as the control group. Co-treatments of DCN with referral drugs were also provided to chicks to evaluate the modulatory action of the test compound. According to the results, DCN delayed the emetic onset and decreased the frequency of retches in a dose-dependent manner compared to the vehicle group. DCN (50 mg/kg) represented a notable delayed latency period (61.17 ± 4.12 s) and a diminished number of retchings (17.67 ± 1.82 times) compared to the control group. Further, in the co-treatments, DCN increased the latency period and reduced the number of retches, except for domperidone. In the *in silico* investigation, DCN showed notable binding affinity toward the D_2 (−7 kcal/mol), H_1 (−7.5 kcal/mol), and M_5 (−7 kcal/mol) receptors in the same binding site as the referral ligand. Our research indicates that DCN has mild antiemetic properties by interacting with the D_2, H_1, and M_5 receptors. Therefore, several pre-clinical and clinical studies are necessary to assess the effectiveness and safety profile of this food ingredient.

1. Introduction

Vomiting, also known as emesis, is an uncomfortable condition in which the stomach fluids are violently evacuated *via* the mouth. It has a close relationship to the gastrointestinal system's motion (Hasler, 2013). Vomiting is triggered by stomach irritants in the gut lumen *via* the gastrointestinal tract's (GIT) thin mucosal chemoreceptors or toxins in the gut lumen (Furness, Rivera, Cho, Bravo, & Callaghan, 2013; Xie et al., 2022). In addition to absorbing poisons or irritants, various illnesses, including poisoning from food, gastroenteritis (diarrhea),

Abbreviations: DCN, dihydrocoumarin; PC, positive control; GIT, gastrointestinal tract; VC, vomiting center; CTZ, chemoreceptor trigger zone; NTS, nucleus tractus solitaries; CSF, cerebrospinal fluid; NK1, neurokinin type 1; 5HT, serotonin; DOM, domperidone; HYO, hyoscine butyl bromide; APR, aprepitant; DHM, diphenhydramine; OND, ondansetron; DW, distilled water; SEM, standard error of the mean; PDB, protein data bank; HB, hydrogen bond; MW, molecular weight; HBD, hydrogen bond donors; MR, molar refractivity; HBA, hydrogen bond acceptor; BBB, blood brain barrier.

* Corresponding authors at: Bioinformatics and Drug Innovation Laboratory, BioLuster Research Center Ltd., Gopalganj 8100, Dhaka, Bangladesh.
E-mail addresses: shimulbhuia.pharm@gmail.com (Md.S. Bhuia), sansari@ksu.edu.sa (S.A. Ansari), dmt.islam@bsmrstu.edu.bd (M.T. Islam).
[1] Equally contributed.

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