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Short communication

In silico prediction of physicochemical, pharmacokinetic and toxicological properties of sulforaphane

Katarina Živančević[1,2*], Dragica Bozic[1], Katarina Baralić[1], Marijana Ćurčić[1], Evica Antonijević Miljaković[1], Biljana Antonijević[1], Danijela Đukić-Ćosić[1]

[1] *University of Belgrade – Faculty of Pharmacy, Department of Toxicology "Akademik Danilo Soldatović", Vojvode Stepe 450, 11000 Belgrade, Serbia*
[2] *University of Belgrade – Faculty of Biology, Institute of Physiology and Biochemistry "Ivan Djaja", Center for Laser Microscopy, Studentski trg 16, 11158, Belgrade, Serbia*

Introduction

Cancer is a major cause of morbidity and mortality worldwide. It is the second leading cause of death in Europe and the leading cause of death in old age. As a cellular disease with multiple genetic and/or epigenetic causes, cancer results in cellular homeostasis disruption and loss of control over cellular proliferation (Elkashty and Tran, 2021). Since different stages of cancer encompass different disturbed signaling pathways including transformation, apoptosis deregulation, proliferation, invasion, angiogenesis, and metastasis (Bayat Mokhtari et al., 2018), an effective therapeutic agent should be able to act at all the different stages (Elkashty and Tran, 2021). Additionally, drug resistance and serious side effects such as liver damage, bone marrow suppression, and neurotoxicity caused by chemotherapy amplified the necessity for more effective drugs with fewer side effects in comparison to existing therapy (Wu et al., 2020). In this context, phytochemicals, such as sulforaphane (SFN), are receiving great attention, due to their ability to modulate multiple targets involved in the carcinogenetic process (Lenzi et al., 2014).

There is a body of evidence that SFN, an isothiocyanate compound present in cruciferous vegetables, inhibits the progression of promyelocytic leukemia, skin, bladder, prostate, colon, pancreatic, liver, lung, nasopharyngeal, ovarian, breast and cervical cancer (Gao et al., 2021). Sulforaphane may inhibit the proliferation and malignant transformation of cancer cells, production of reactive oxygen species, cytochrome P450 3A4 and phase I metabolism enzymes, G1 to S phase progression and G2/M phase arrest and activate apoptotic pathways (Gao et al., 2021).

Since to date, broccoli seed extract has been used in clinical trials, data on the toxic potential of chemically synthesized SFN are very limited and it is necessary to examine its toxicological profile in more detail.

The 3R principle in toxicological research forced the development of *in silico* tools which allow preliminary toxicological investigations and shape further *in vitro* and *in vivo* analysis.

Therefore, the aim of this study was to conduct *in silico* prediction of physicochemical and pharmacokinetic properties for the targeted molecule, sulforaphane, in order to better understand its toxicological potential.

Materials and methods

Physicochemical and pharmacokinetic properties were evaluated by SwissADME (http://www.swissadme.ch/), while the assessment of toxic properties based on structure was evaluated by mcule (https://mcule.com/; Toxicity checker tool). ADMETlab 2.0 (https://admetmesh.scbdd.com/) was used to compare results related to physicochemical, pharmacokinetic and toxic properties of SFN.

*kzivancevic@pharmacy.bg.ac.rs

Results and discussion

According to the SwissADME analysis, SFN was in the optimal range for lipophilicity, size, polarity, solubility, saturation and flexibility, which indicates that it is orally bioavailable. Also, these results indicated that passive human gastrointestinal absorption (HIA) is high, that SFN is not blood brain barrier (BBB)-permeant and that it is not P-glycoprotein substrate. Additionally, this analysis showed that SFN does not inhibit CYP1A2, CYP2D6, CYP3A4, CYP2C19, CYP2C9. On the contrary, ADMETlab 2.0 evaluation showed differences in BBB permeability, which was rated as medium, and SFN was rated as CYP2C19 substrate. Also, it showed that SFN is neither P-glycoprotein substrate nor inhibitor.

SwissADME analysis based on different rule-based filters (Lipinski, Ghose, Veber, Egan) has shown that SFN is considered drug-like substance, while according to the Muegge filter, there is one violation (molecular weight < 200). ADMETlab 2.0 drug-likeliness evaluation of SFN was accepted based on Lipinski, Pfizer, GSK filter, while the concept of desirability, 3D complexity and novelty, as well as Golden Triangle rule assessed that SFN have poor ADMET profile. This evaluation also considered clearance of SFN as moderate (6.775 ml/min/kg) and the half-life of SFN was predicted to be < 3 hours.

However, medicinal chemistry SwissADME analysis showed that, due to its molecular weight < 250, SFN may exert violations to the lead-likeness indicators. Also, two structural alerts were detected (imine and thiocarbonyl group). ADMETlab 2.0 has also indicated alerts for Genotoxic Carcinogenicity (2), NonGenotoxic Carcinogenicity (1), Skin Sensitization (3), Aquatic Toxicity (2). According to SureChEMBL Rule and FAF-Drugs4 Rule, SFN has MedChem unfriendly status and potentially toxic substructures. These results suggest that the route of drug administration and its formulation should be optimized and that analogues of SFN with some structural modifications could be considered during the drug discovery process. Special attention should be paid in the case of further substituents insertion on SFN structure, particularly in the case of orally administered drugs. Additionally, SwissADME Synthetic accessibility tool demonstrated that SFN is a molecule which should be prioritized for synthesis, considering the value of its SA score (3.07) which was supported with ADMETlab 2.0 analysis (SA score = 4.972).

Based on toxic matching rules analysis provided by mcule, SFN contains potential promiscuous substructure (mcule, Toxicity checker tool). ADMETlab 2.0 toxicity prediction analysis revealed medium probability for drug-induced liver injury development and dermal adverse effects. It also showed probability for Ames toxicity (mutagenicity), Rat Oral Acute Toxicity, Carcinogencity, Eye Corrosion, Eye Irritation and Respiratory Toxicity.

ADMETlab 2.0 Tox21 Pathway analysis pointed out the aryl hydrocarbon receptor, the antioxidant response element signaling pathway, heat shock factor response element, mitochondrial membrane potential, which had the high probability of being active, while aromatase, estrogen receptor and tumor suppressor protein p53 were of medium probability of being active.

Conclusion

This short *in silico* study reported significant variability in prediction of physicochemical and pharmacokinetic properties as well in toxicological potential of SFN, using different tools. Although, SFN demonstrated high capability to inhibit metastases in different tumor models, larger-scale of *in silico* and toxicity studies are necessary to further examine its toxicological profile.

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