Original Research Article

An *In-Silico* Pharmacokinetics Study on Cis-Heptadeca-1,9-Diene-4,6-Diyne-3,8-Diol: A Nutraceutical Compound with Anticancer Properties

Abstract

The polyacetylenic compound cis-heptadeca-1,9-diene-4,6-diyne-3,8-diol with the trivial name of falcarindiol, has been shown through various studies to exhibit anticancer activities. The beneficial effects of polyacetylenes occur at nontoxic concentrations and thus represent pharmacologically useful properties indicating that polyacetylenes may be important nutraceuticals of vegetables. In the human diet, carrots are the major dietary source of falcarinol-type polyacetylenes, in particular falcarinol and falcarindiol. The prediction of physicochemical parameters relevant for drug likeness was performed by computational methods. The Lipinski, Ghose and Veber rules were applied to assess drug likeness and to predict whether the compound is likely to be a bioactive compound according to other important parameters such as molecular weight, LogP, number of hydrogen bond donors and hydrogen bond acceptors. The SwissADME tool used vector machine algorithm (SVM) with fastidiously cleaned large datasets of known inhibitors/non-inhibitors as well as substrates/non-substrates for its predictions. Results from the *in silico* pharmacokinetics study on falcarindiol showed that the compound exhibited drug likeness characteristics and as such can serve the purpose of an anticancer agent, being a nutaceutical and bioactive component of falcarindiol.

Keywords: Falcarindiol; Polyacetylenes; Lipinski; Ghose; Pharmacokinetics

Introduction

Epidemiological studies have provided evidence that a diet high in fruit and vegetables is associated with a reduced risk for the development of certain types of cancer, cardiovascular diseases, diabetes, and other diseases [1]. Compounds associated with the health promoting effects of vegetables are glucosinolates and other organosulfur compounds and their degradation products, carotenoids, phytosterols, polyphenols, vitamins, and dietary fibers [2]. The mechanisms for the protection of these classes of natural products are mostly unknown and may only in part explain the health effects of vegetables. Consequently, in recent years focus has been on other types of potential health promoting compounds [3].

Falcarindiol (FAD) is a natural polyyne found in vegetables and it has been shown to have anti-inflammation, antibacterial and anticancer activities, as well as protective effects against hepatotoxicity. Moreover, these beneficial effects occur at non-toxic concentrations and thus represent pharmacologically useful properties [4, 5]. In particular, the anti-proliferative and antitumor functions of FAD were confirmed repeatedly, in colon cancer and breast cancer cells but unfortunately, however, there is little research on the consequence of FAD treatment in the fate determination of stem cells [6, 7, 8, 9].

Falcarindiol has also been isolated from *Aegopodum podraria L*., and its antifungal activity towards some other fungi noted [10]. Various other Umbelliferae, *Apium graveolens L., Falaria vulari Bernh., Oenanthe crocata L. and Opanax chironium Koch*. also produce falcarindiol [11].

A good number of other acetylenic compounds isolated from di□erent plant families have also been shown to exhibit antifungal activities [12, 13]. The few antifungal polyacetylenic compounds that have been investigated appear to be important in disease resistance and since polyacetylenes are widespread in plants, the group as a whole may subsequently be found to be of importance as suggested by Overeem (1976) [14].

This study is therefore aimed at predicting the pharmacokinetics parameters of falcarindiol for the confirmation of its drug likeness properties using specific computational biology approach.

Materials and Methods

In silico ADMET screening

The ADMET properties including aqueous solubility, blood brain barrier (BBB), plasma protein binding, CYP2D6 binding, gastrointestinal absorption and hepatotoxicity were evaluated for these molecules within human. The models used to predict the ADMET properties in this protocol are derived from a variety of experimental data sources and are catalogued in the product documentation [15].

Screening for Pharmacokinetics and Drug-likeness

Pharmacokinetics and drug-likeness prediction for falcarindiol was also performed using an online tool SwissADME [16] of the Swiss Institute of Bioinformatics (http://www.sib.swiss). This was used to evaluate individual ADME behaviors of the compound [17].

In the Swiss ADME program package, the topological polar surface area (TPSA) was calculated according to Ertl *et al* [18]. Furthermore, the lipophilicity was predicted according to Wildman et al. [19], the solubility was predicted according to Ali *et al* [20], and violations of the Pfzer flter for oral bioavailability were assessed according to Lipinski *et al* [21]. Results are indicated in Figure 3.

The analysis task was done to check whether falcarindiol was an inhibitor of isoforms of Cytochrome P450 (CYP) family such as CYP1A2 and CYP2D6. In addition to other predicted pharmacokinetics (such as gastro intestinal absorption, P-glycoprotein and Blood brain barrier) and drug-likeness prediction such as Ghose and Veber rules and the bioavailability score [22, 23].

2D Structure Modeling and File Conversion

2D structural models were drawn in MarvinSketch (ChemAxon Software) and the falcarindiol SMILES was translated into a mol2 file by online SMILES translator and structure file generator found in the OpenBabel software [24].

Ligand Minimization

Falcarindiol 3D structure was minimized using the UCSF Chimera software [25]. UCSF Chimera is an extensible program for analyzing and interactively visualizing molecular structures and related data which include supramolecular assemblies, density maps, alignment of sequences, results from molecular docking trajectories and conformational ensembles [26].

Visualization of Atoms

Atoms making up falcarindiol was visualized using the Pymol molecular visualizer [27]. PyMOL is an open-source tool for model visualization and it is made available for utilization in structural biology [28]. The *Py* aspect of the name of the software is a reference pointer that it is extensible and extends by the python programming language [29].

Results and Discussion

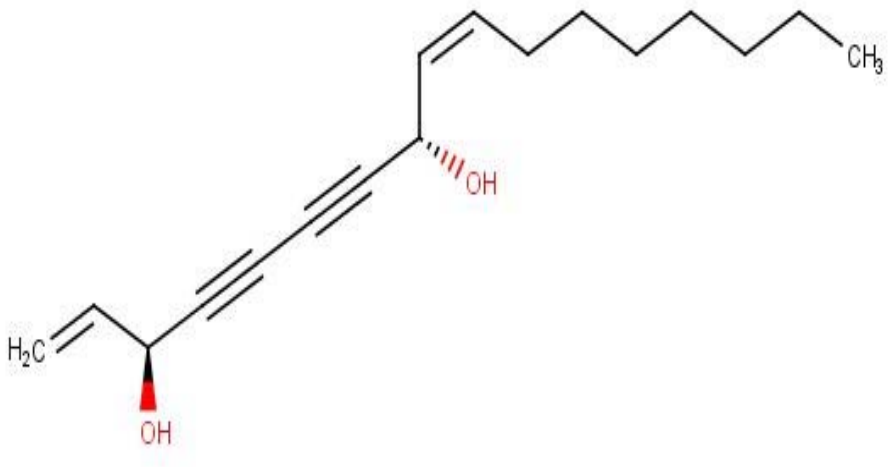

Figure 1: 2D Structure of Falcarindiol

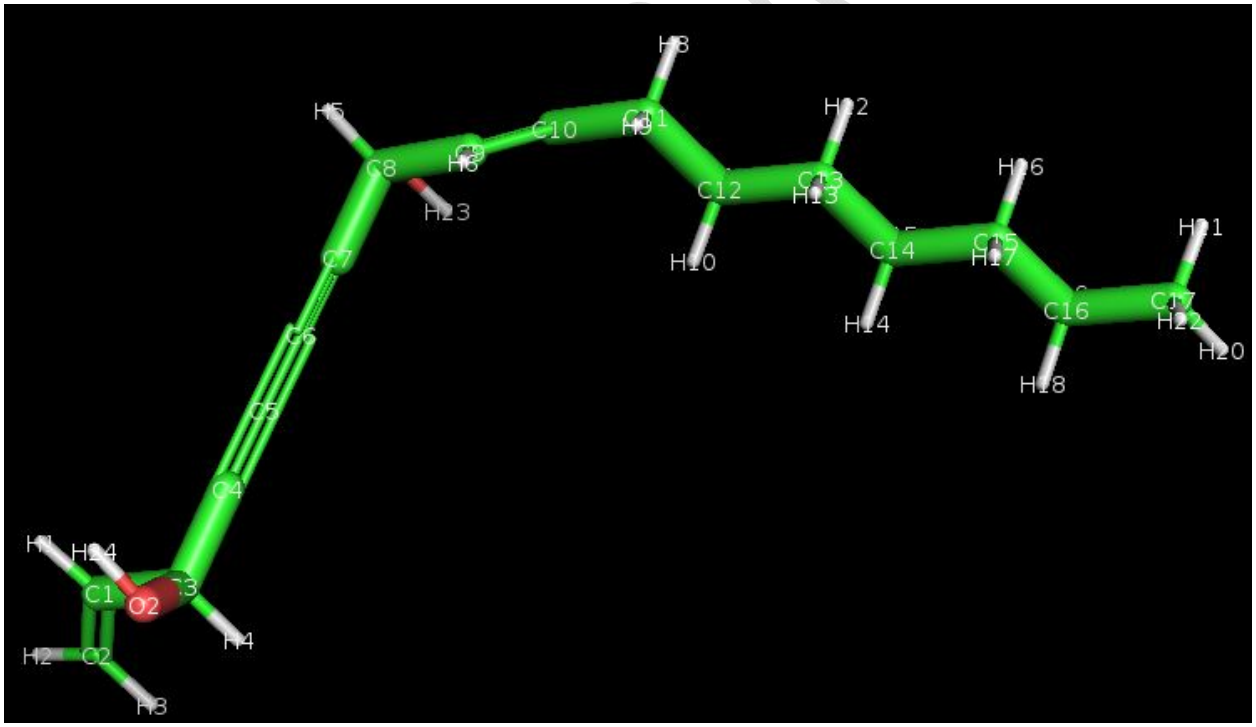

Figure 2: Minimized 3D structure of Falcarindiol with Labeled Atoms

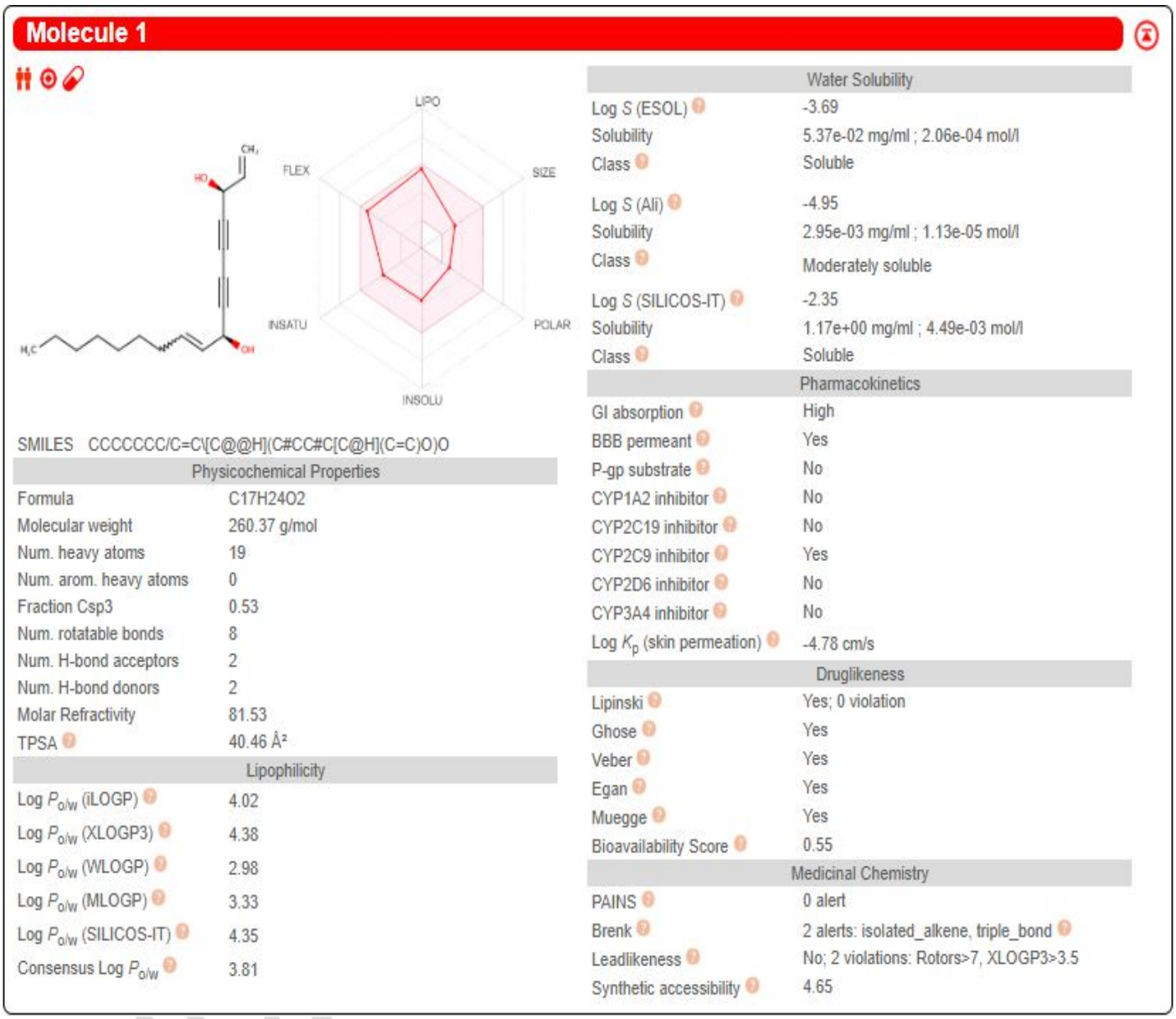

Figure 3: SwissADME *In Silico* Pharmacokinetics Result for Falcarindiol

In this study, we subjected the designed falcarindiol chemical structure to *in silico* ADMET screening, using the SwissADME online software, to predict the overall absorption, distribution, metabolism, excretion, and toxicity risks. In the *in silico* evaluation, the analysis of different descriptors (calculated octanol/water partition coefficient, molecular weight, molecular volume, number of hydrogen bond donors and acceptor groups) of all compounds revealed that they are highly hydrophobic to penetrate the biological membranes, as determined by the Lipinski "rule-of-five" which states that the absorption or permeation of a molecule is more likely when the molecular weight is under 500 g/mol, the value of log P is lower than 5, and the molecule has utmost 5 H-donor and 10 H-acceptor atoms (cLogP<5, MW>500, HBD<5 and HBA<10) [21,

30] as shown in Figure 3. The Lipinski (Pfzer) filter is the pioneer rule-of-five [31], therefore, this result suggests that falcarindiol have a high theoretical oral bioavailability.

According to the pharmacokinetic properties, falcarindiol showed a high gastrointestinal absorption property which gives credence to it oral bioavailability score. Falcarindiol according to the *in silico* pharmacokinetics report possess the blood brain barrier permeability attribute but it however showed no inhibition to the Cytochrome P450 isomers and the P-glycoprotein with the exemption of the CYP2D6 isomer. The drug-likeness prediction was also conducted depending on the selected Ghose, Veber rules and bioavailability score.

The Ghose filter (Amgen) [22] defines drug-likeness constraints as follows: calculated log P is between -0.4 and 5.6, MW is between 160 and 480, molar refractivity is between 40 and 130, and the total number of atoms is between 20 and 70. Veber (GSK) [23], rule defines drug likeness constraints as Rotatable bond count ≤ 10 and polar surface area (PSA) ≤ 140. Just as the screening process with Lipinski Rule of Five showed that there were no compound violations, suggestions according to the screening process with Ghose rules show that falcarindiol can be accepted as it showed no violations (Figure 3). Also, the screening process with Veber rules showed that falcarindiol met the criteria for drug likeness assessment. Using the above models also indicate that falcarindiol violates none of the standards defined by each drug likeness prediction model

The Bioavailability score was implemented without changes from Martin *et al*., and it is similar but seeks to predict the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability [32].

Conclusion

The computational analysis on the pharmacokinetics and drug likeness parameters of falcarindol has confirmed the safety of the compound for oral administration. Haven shown the ability to cross the blood brain barrier as seen in the above results, falcarindiol can only be administered as a neuroactive drug to avoid side effects as regarding the central nervous system.

The synthetic accessibility score of falcarindiol has also shown that it falls within the range of compounds that can be easily synthesized. We therefore recommend the laboratory synthesis of falcarindiol for further studies such as the molecular docking with structural modifications and preclinical trials.

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