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ADME Webtool for Analysis of Selected Apple Phytochemical Constituents: A Comprehensive Integrated Online Platform

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ABSTRACT

ADME-Tox qualities should be considered while designing/engineering a novel medicine because they are the primary cause of failures for candidate molecules in drug design development. Early examination of these features during medication creation might save time and money. ADME has played an important part in the drug engineering/design process throughout the last five decades. The ADME characteristics of apple constituents were determined using SwissADME web servers. The ADME profiles of the compounds were assessed, and most of them were deemed to be appropriate for further research. *In-silico* ADMET analysis has been shown to be an effective approach in drug engineering/design development. As a result, all compounds were tested for ADMET prediction, and the phytochemical constituents were shown to be acceptable drug-like molecules. More *in vitro* and *in vivo* research with our possible phytochemical compounds will be conducted in the near future to find a solution to cure different diseases.

Keywords: SwissADME, ChemDraw, *in silico* prediction, ADME-Tox, Design, Medicine.

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Introduction

ADME stands for absorption, distribution, metabolism, and excretion. It describes the pharmacokinetics of a pharmacological molecule. There have been multiple reports of drug development efforts being abandoned due to poor ADME profiles [1]. ADME profiling was shown to be more effective prior to synthesis and *in-vivo* research. The determination of ADME characteristics of substances necessitates a slew of time-consuming and costly experimental techniques. As a result, *in sillco* ADME models have been created. SWISS ADME predictor [2] was used for the ADME investigation. The latter is considered a free tool (web) that is used for estimating the drug similarity, pharmacokinetics, as well as medicinal chemistry of small compounds. As previously stated, emphasis was placed on designing molecules that adhered to the criterion of drug-likeness [[3], [4]].

Log P is a measure used to estimate a molecule's lipophilicity and can be defined as the logarithm of the ratio of drug concentration among two unionized solvents [5]. The Lipinski rule establishes a maximum limit of 5 for druggable substances. It is well known that the lower log P values indicate the higher lipophilicity of the drug. A compound's water solubility has a large impact on its absorption as well as distribution properties. On the other hand, low water solubility relates to weak absorption, therefore the overall goal is to avoid weakly soluble substances. Log S is defined as a unit to represent solubility which is the 10-based logarithm of solubility and measured in unit mol/L. The Log S distribution in traded medications indicates a value ranging from -1 to -4, which will be ideal for improved drug absorption and distribution in the body [[3], [4]].

Food offers not only the necessary nutrients needed for a living but also additional chemicals for promoting health and preventing disease since it is a

complex mixture of a broad range of components, many of which are biologically active. Nutrients are a group of previously identified substances that are crucial for the body's development, maintenance, and repair. Previous epidemiologic studies have repeatedly demonstrated the critical impact that nutrition plays in preventing chronic illnesses [6]. Remarkably, according to research, a diet high in fruits and vegetables may reduce the risk of chronic illnesses such as cancer and cardiovascular disease.

The bioactive components in these natural products—dietary fiber and antioxidants, namely phenolic compounds, flavonoids, phenolic acids, etc.—are thought to be what give them their beneficial effects [7]. Therefore, there is presently a lot of interest in the numerous bioactive substances that may be found in food, especially food that comes from plants. These plant-based bioactive substances are usually referred to as phytochemicals [8]. Although it is considered that more than 5000 phytochemicals have been found, a significant portion is still unknown and needs to be discovered before their health advantages can be properly comprehended.

The advantages of phytochemicals in fruit and vegetables may, however, be much higher than currently believed since oxidative stress brought on by free radicals is thought to be a contributing factor in the development of a wide range of chronic illnesses [9]. Due to their content of phytochemicals, several frequently eaten foods and drinks have been identified as particularly advantageous in the diet. Although there has been continuing study into the health benefits of these foods, there are now available evaluations of this work for all save apples [10].

Because of a variety of variables, including market accessibility and cultivar variation, apples make up a significant amount of the fruit supply throughout the year in most nations [11]. The adage "one apple a day, keeps the doctor away" refers to the widespread consumption of apples and their overall health benefits. What is less generally recognized, though, is that apples are a good source of strong plant components such as phytochemical constituents (Figure 1), and epidemiological findings have connected apple consumption to a minor risk of some malignancies, cardiovascular disease, diabetes, and asthma [10].

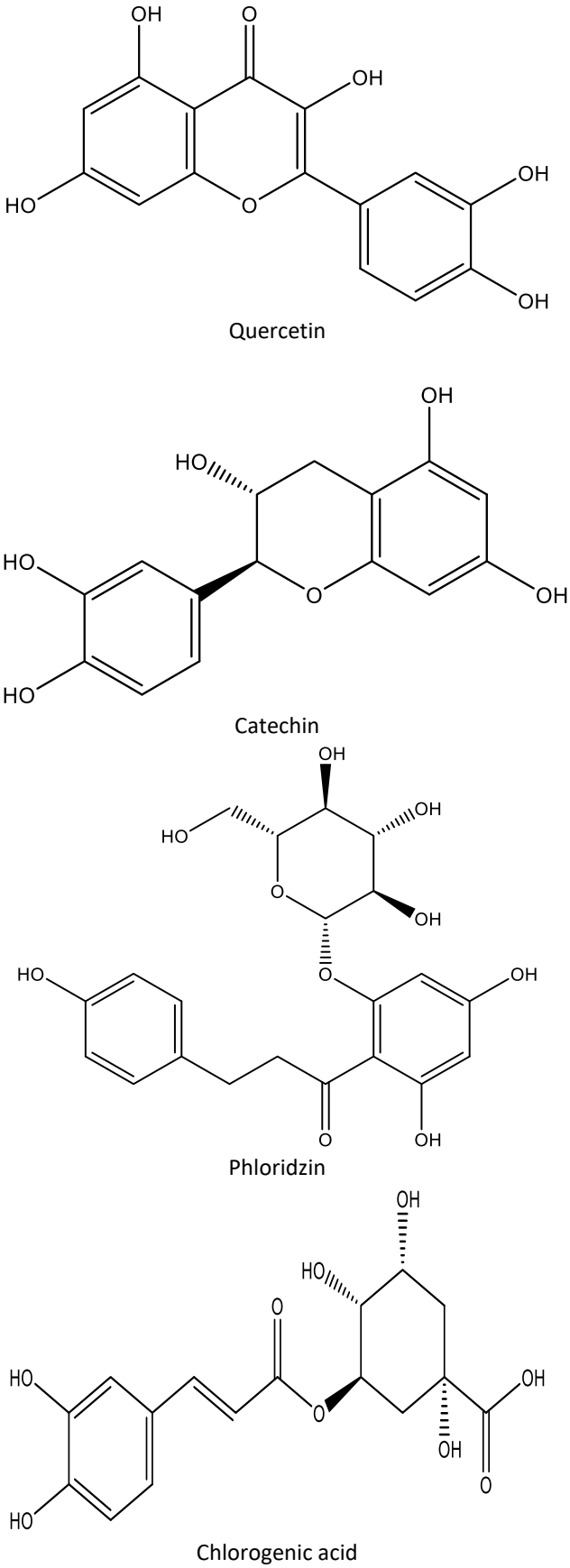

Figure 1 - Chemical structures of some phytochemical constituents in apple

ADME properties calculation

The structure was created in Chemsketch, and the SMILES of each chemical were translated into molfiles using an online SMILES translator and structure file generator available in the online program SwissADME. Furthermore, pharmacokinetics such as gastrointestinal absorption, skin permeability, blood-brain barrier, as well as a drug-likeness estimate for instance bioavailability score.

BBB penetration is a parameter used to determine if a substance passes via the blood-brain barrier. Numerous drugs must not cross over the blood-brain barrier if the aim is unrelated to the nervous system [12].

The skin permeability of the substance is a significant feature regarding the adverse reaction of the drug in the case of pharmaceuticals taken orally to identify of accidental contact with skin and the skin permeability of drugs to be administered transdermally where skin penetration is a significant aspect. The result value of a compound's skin permeability is provided such as log Kp. Kp [cm/hour] is described as Kp= Km*D/h, where Km is called the distribution coefficient between the vehicle and the stratum corneum, D is defined as the average diffusion coefficient [cm^2/h], and h is the skin thickness [cm] [4].

The knowledge of chemicals that are considered either a substrate or a non-substrate of the permeability glycoprotein. It refers to the most significant ABC transporter, which is vital for evaluating active efflux through biological membranes, for example from the wall of the gastrointestinal to the lumen or even from the brain. P-gp shields the central nervous system against xenobiotics. Additionally, P-gp is overexpressed in specific cancer cells, which leads to tumors in multidrug-resistant [13].

Drug-likeness is considered a qualitative evaluation of a molecule's chances of becoming an oral drug by means of bioavailability. Drug-likeness resulting from physicochemical or structural examinations of research compounds progressed sufficiently to be considered oral drug candidates. This concept is commonly used in the filtering of chemical libraries to refuse compounds with characteristics that are most probable incompatible with an appropriate pharmacokinetics profile [[4], [14]]. The current SwissADME section offers full access to five alternative rule-based filters together with changing ranges of attributes within which the molecule is regarded as drug-like. These filters are frequently produced by pharmaceutical corporations to enhance the quality of their chemical collections. The Lipinski (Pfizer) filter was the first to include the Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) technologies [15].

A soluble molecule significantly simplifies several drug development procedures, particularly the simplicity of processing and formulation. Solubility is an important property that influences absorption in drug discovery plans aimed at oral administration, and drugs aimed for parenteral administration must be very water soluble to deliver an adequate amount of active ingredient in the minor volume of pharmaceutical dosage. SwissADME includes two topological approaches for predicting solubility in water.

The first model is called ESOL model implementation, whereas the second one is adapted from Ali et al. modification. Both differ from the fundamental universal solubility equation by omitting the difficult-to-estimate melting point parameter. They show a significant linear connection between anticipated and observed values (R^2=0.69 and 0.81, respectively). SILICOS-IT created the SwissADME third predictor for solubility. This fragmental method's linear correlation coefficient adjusted for molecular weight is R^2 = 0.75. To calculate all expected values (log S), the decimal logarithm of the molar solubility in water is used. Additionally, SwissADME offers solubility in mol/l and mg/ml units, as well as solubility classes [[4], [16], [17], [18], [19], [20], [21] [22], [23]].

Results and Discussion

Table 1 shows the IUPAC name and the SMILES code of some phytochemical constituents of apples. SwissADME online version was used to estimate the pharmacokinetic characteristics and drug-likeness of apple phytochemical ingredients, and the results are displayed in table 2 and table 3, respectively. All test substances demonstrated pharmacokinetic characteristics. The bioavailability score predicted medication similarity in moderately soluble and soluble gastrointestinal absorption.

Table 1 - The IUPAC name and the SMILES code of some phytochemical constituents of apple

No.	Phytochemical Constituents	IUPAC Name	Canonical SMILES
1	Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7trihydroxychromen-4-one	CC1CCC2C(C(=O)OC3C24C1CCC(O3)(OO4)C)C
2	Catechin	(2S,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
3	Phloridzin	1-[2,4-dihydroxy-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]-3-(4-hydroxyphenyl)propan-1-one	C1=CC(=CC=C1CCC(=O)C2=C(C=C(C=C2OC3C(C(C(C(O3)CO)O)O)O)O)O)O
4	Chlorogenic acid	(1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid	C1C(C(C(CC1(C(=O)O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O

Table 2 - Pharmacokinetics and drug-likeness prediction of some Phytochemical constituents of apple

No.	Phytochemical Constituents	Pharmacokinetics			Drug-likeness
		GI Absorption	BBB Permeability	Log Kp (skin Permeation) cm/s	Bioavailability Score
1	Quercetin	High	Yes	-5.96	0.55
2	Catechin	High	No	-7.82	0.55
3	Phloridzin	Low	No	-8.58	0.55
4	Chlorogenic acid	Low	No	-8.76	0.11

Table 3 - Water solubility prediction for some Phytochemical constituents of apple

No.	Phytochemical constituents	LogP	Water Solubility		
		(Consensus LogP)	LogS (ESOL)	LogS (Ali)	LogS (SILICOS-IT)
1	Quercetin	2.50	-3.42	-3.69	-2.03
2	Catechin	0.85	-2.22	-2.24	-2.14
3	Phloridzin	0.08	-2.71	-3.83	-1.66
4	Chlorogenic acid	-0.57	-1.62	-2.58	0.40

Conclusions

According to Lipinski's rule-of-five (RO5), all phytochemical elements of apple displayed strong drug-likeness and were projected to be BBB non-permeant (blood-brain barrier), implying no expected neurological adverse effects. It has been demonstrated that it has a high bioavailability, implying that the molecules could be absorbed and transported throughout the body if used as a

medication. As a result, all compounds were examined for ADMET prediction, and the Phytochemical ingredients were found to be acceptable drug-like molecules.

Conflict of interest

The correspondent author declares that there is no conflict of interest on behalf of all authors.

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Алманың таңдалған фитохимиялық құрамдас бөліктерін талдауға арналған ADME веб-құралы: кешенді біріктірілген онлайн платформа

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ТҮЙІНДЕМЕ

ADME-Tox қасиеттерін жаңа препараттарды жасағанда, өндіргенде ескеру қажет, себебі бұлар дәрілік заттарды әзірлеу кезінде кандидат-молекулалар үшін болатын сәтсіздіктерінің негізгі себебі болып табылады. Дәрі-дәрмектерді дайындағанда бұл сипаттамаларды мерзімінен бұрын зерттеу - уақыт пен ақшаны үнемдеуге мүмкіндік береді. ADME соңғы бес онжылдықта дәрілерді жасағанда маңызды рөл атқарады. Алмалардың ADME сипаттамалары SwissADME серверлерінің көмегімен анықталды. ADME қосылыстарының профильдері бағаланды және олардың көпшілігі қосымша зерттеулер үшін жарамды деп саналды. In-silico ADMET талдауы дәрілік инженерия/дизайн әзірлеуде тиімді тәсіл екені көрсетілді. Нәтижесінде барлық қосылыстар ADMET болжамы үшін сыналған және фитохимиялық құрамдастардың қолайлы дәрілік молекулалар екендігі көрсетілген. Жақын арада әртүрлі ауруларды емдеудің шешімін табу үшін біздің ықтимал фитохимиялық қосылыстарымызбен in vitro және in vivo зерттеулері жүргізіледі.

Түйін сөздер: SwissADME, ChemDraw, *in silico* болжау, ADME-Tox, дизайн, медицина.

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Веб-инструмент ADME для анализа выбранных фитохимических компонентов яблока: комплексная интегрированная онлайн-платформа

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АННОТАЦИЯ

Свойства ADME-Tox следует учитывать при разработке/производстве новых лекарств, поскольку они являются основной причиной неудач для молекул-кандидатов при разработке лекарств. Преждевременное изучение данных характеристик дает воможность сэкономить время и деньги при создании лекарственных препаратов. ADME играет важную роль в процессе разработки лекарств на протяжении последних пяти десятилетий. Характеристики ADME яблок были определены с использованием серверов SwissADME. Были оценены профили ADME соединений, и большинство из них было сочтено

	подходящими для дальнейших исследований. Было доказано, что анализ *In-silico* ADMET является эффективным подходом при производстве/разработке лекарств. В результате всех соединений были протестированы на предсказание ADMET, и было показано, что фитохимические соединения являются приемлемыми лекарственными молекулами. В ближайшем будущем будут проведены дополнительные исследования in vitro и in vivo с учетом возможных фитохимических соединений, чтобы найти решение для лечения различных заболеваний.
	Ключевые слова: SwissADME, ChemDraw, *in silico* прогнозирование, ADME-Tox, дизайн, медицина.
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