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In Silico Comparison of Drug-Likeness of Phytochemicals from Nine Herbal Plants against Asthma †

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Abstract: Asthma is a chronic obstructive pulmonary disease, affecting approximately 300 million people worldwide. Current therapies have disadvantages like side effects and high costs. Alternatively, herbal plants have been used for decades as focal medicine to cure asthma. The goal of this research was to make use of molinspiration and pkCSM in silico tools to determine the drug-likeness of nine phytochemicals (Mangiferonic acid, Withaferin A, Stigmasterol, 6-Shogaol, Rosmarinic acid, Glycyrrhizin, Alphitolic acid, Oleanic acid, and Kalambroside A) present in nine distinct herbal plants. These phytochemicals have reported anti-asthmatic properties. Currently, available fluticasone propionate drug was used as the positive control. Molinspiration findings showed that except for glycyrrhizin and Kamabroside A, all other phytochemicals obeyed Lipinski's and Verber's rules. Furthermore, all phytochemicals except glycyrrhizin and Kalambroside A exhibited considerable bioactivity for nuclear receptors (NRs) with bioactivity scores ranging from 0.20 to 0.96. The pkCSM results indicated that mangiferonic acid, withaferin A, 6-Shogaol, and stigmasterol exhibit high intestinal absorption (>80%), high Caco-2 permeability (log Papp > 0.90 × 10^{-6} cm/s), high lethal dose (LD_{50} = 2.081 to 3.201 mol/kg), non-mutagenicity, and non-hepatotoxicity. Furthermore, these phytochemicals were non-inhibitors of cytochrome P450 enzymes. In conclusion, mangiferonic acid abundantly available in *Pericampylus glaucus* is regarded as the best phytochemical that can be developed into a drug against asthma. Since it had good bioavailability, considerable bioactivity towards NRs, and higher LD_{50} than the control drug. However, further wet-lab experiments are required to develop mangiferonic acid as a potent anti-asthmatic drug.

Keywords: asthma; drug-likeness; phytochemicals; mangiferonic acid

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1. Introduction

Asthma is a chronic obstructive pulmonary disease, affecting approximately 300 million people worldwide. Inhaled corticosteroid (ICSs) remains the mainstay treatment for persistent asthma. However, long-term use of ICS results in systemic side effects such as growth retardation in children, suppression of the hypothalamus-pituitary-adrenal axis, osteoporosis, cataract formation, and early bruising [1]. Therefore, scientists are seeking alternative treatments for asthma. Herbal plants have been used for decades as focal medicine to cure asthma. It is highly preferred over conventional medicines due to its various health benefits, lack of toxicity, and side effects.

Herbal plants including Pericampylus glaucus, Withania somnifera (l.) Dunal, Zingiber officinale Roscoe, Origanum vulgare, Glycyrrhiza glabra, Ziziphus amole, Achyranthes aspera and Kalanchoe laciniata have proven to have anti-asthmatic properties [2–8]. These herbal plants have valuable phytochemicals which have anti-inflammatory, antiallergic, and antioxidant properties (Figure 1).

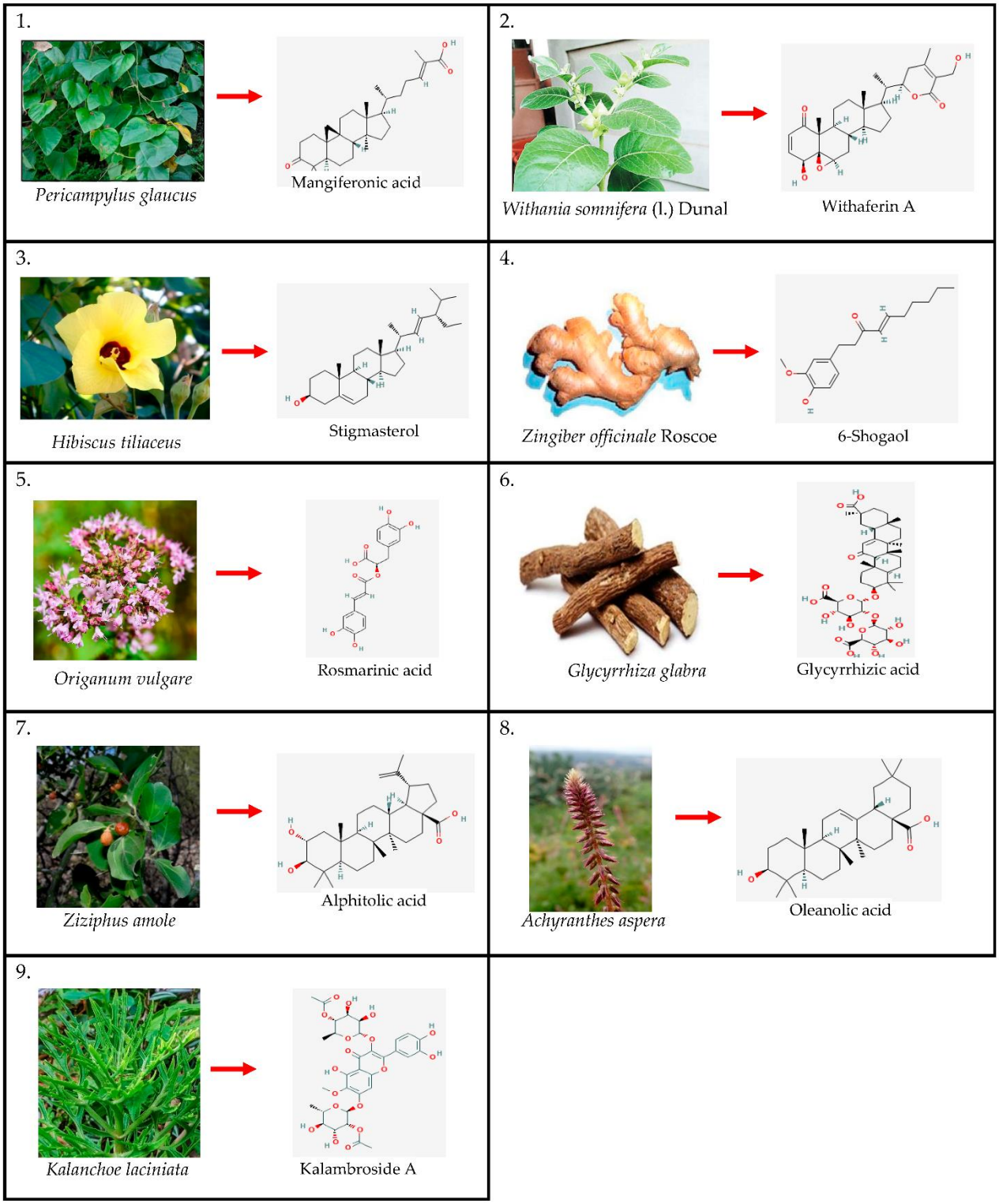

Figure 1. List of 9 different herbal plants and their phytochemical structures [9].

In order to ensure that these phytochemicals are eligible for oral use, their drug-likeness properties need to be evaluated. "Drug-likeness" is a qualitative concept used in drug design to assess the chance of a molecule becoming an oral drug and it is estimated from the structure and/or physiochemical properties of the chemical compound [10]. In silico tools are widely used to determine the drug-likeness as they aid in predicting promising

drug candidates which are safe and effective to be used in humans prior to wet lab experiments namely, preclinical and clinical trials. Thereby, it helps to minimize the time and cost of the drug discovery process [11].

In silico tools make use of existing information derived from the molecular structure to make predictions on the pharmacokinetic properties such as ADME (absorption, distribution, metabolism, and excretion) which determine the internal exposure and biological activity (toxicity or hazard) of a chemical [12]. The aim of this research is to determine the drug-likeness of these phytochemicals using molinspiration and pkCSM online web tools. Also, to identify the best phytochemical that is suitable to become oral anti-asthmatic drugs.

2. Methodology

In this research, fluticasone propionate was used as the standard control drug and the drug-likeness of each phytochemical was compared with this drug, to select the best phytochemical. Firstly, the canonical Simplified Molecular Input Line Entry System (SMILES) of phytochemicals and fluticasone propionate were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Then, each canonical SMILES was entered into the molinspiration by accessing this link (https://www.molinspiration.com/). Molinspiration software was used for the calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors), and prediction of bioactivity score for the most important drug targets (in this case, the nuclear receptors) [13]. To determine whether these phytochemicals have good oral bioavailability, Lipinski's and Verber's rules were applied to the results obtained from molinspiration. Afterward, to predict the pharmacokinetics and toxicity properties, canonical SMILES of each compound were entered into the pkCSM tool (http://biosig.unimelb.edu.au/pkcsm/prediction) [14].

3. Results and Discussion

3.1. Molinspiration

Table 1. Physiochemical properties of all phytochemicals and reference drug.

Physiochemical Parameters	Chemical Compound				
	Mangiferonic Acid	**Withaferin A**	**Stigmasterol**	**6-Shogaol**	**Rosmarinic Acid**
miLogP	6.69	3.86	7.87	4.35	1.63
TPSA	54.37	96.36	20.23	46.53	144.52
MW	454.69	470.61	412.70	276.38	360.32
nON	3	6	1	3	8
nOHNH	1	2	1	1	5
nviolations	1	0	1	0	0
nrotb	5	3	5	9	7
Physiochemical Parameters	**Chemical Compound**				
	Glycyrrhizin	**Alphitolic Acid**	**Oleanic Acid**	**Kalambroside A**	**Fluticasone Propionate (Control)**
miLogP	1.97	6.13	6.72	0.84	4.61
TPSA	267.04	77.75	57.53	270.59	80.67
MW	822.94	472.71	456.71	708.62	500.58
nON	16	4	3	18	5
nOHNH	8	3	2	7	1
nviolations	3	1	1	3	1
nrotb	7	2	1	10	6

LogP-lipophilic efficiency; TPSA-topological polar surface area; MW-molecular weight; nON-number of hydrogen bond acceptors; nOHNH-number of hydrogen bond donors; nviolations-number of Lipinski's rule of five violations; nrotb-number of rotatable bonds.

Lipinski's rule states that a molecule having: (1) MW ≤ 500 Da; (2) Log P ≤ 5; (3) nOHNH ≤ 5; and nON ≤ 10 has good in vivo absorption and permeability so it could be a good drug candidate [15]. If any compound has more than 1 violation, then it is considered to have poor absorption and permeability and is excluded from further development [16]. According to the results, except for glycyrrhizin and Kamabroside A, all other phytochemicals and fluticasone propionate obeyed Lipinski's rule. Glycyrrhizin and Kamabroside A had higher MW, nON, and nOHNH than the acceptable range. According to the Verber rule, compounds with TPSA ≤ 140 Å and nROTB ≤ 10 have good oral bioavailability [17]. Except for glycyrrhizin asnd Kamabroside A, all other phytochemicals and fluticasone propionate obeyed Verber's rule.

Table 2. Bioactivity scores of the compounds towards the nuclear receptor.

Chemical Compounds	Nuclear Receptor Ligand
Rosmarinic acid	0.57
6-Shogaol	0.20
Glycyrrhizin	−2.36
Fluticasone propionate	1.83
Kalambroside A	−1.11
Oleanic acid	0.77
Stigmasterol	0.74
Withaferin A	0.76
Mangiferonic acid	0.88
Alphitolic acid	0.96

Nuclear receptors (NR) are the drug targets for asthma and corticosteroids are synthesized to target nuclear glucocorticoid receptors [18]. Therefore, it is crucial to ensure that these phytochemicals possess better bioactivity scores to be considered as drugs. A compound with a bioactivity score greater than 0.00 is likely to exhibit considerable bioactivity, while values between −0.50 and 0.00 are moderately active and if it is less than −0.50, it is presumed to be inactive [19]. These results suggest that all phytochemicals except glycyrrhizin and Kalambroside A, exhibit considerable bioactivity. Among phytochemicals, Alphitolic acid exhibited the highest bioactivity score hence it has the highest activity towards NR. Glycyrrhizin and Kalambroside A are inactive towards NR.

3.2. pKCSM Tool

3.2.1. Absorption

Intestinal absorption (Human)

If the absorption value is more than 80%, it suggests that the absorption capacity is high [20]. A molecule with an absorbance less than 30%, is considered to be poorly absorbed [20]. Oleanic acid, mangiferonic acid, 6-shogaol, stigmasterol, withaferin A, alphitolic acid, and fluticasone propionate have absorption values > 80% hence they can be well absorbed in the intestine. Moreover, alphitolic acid had the highest 100% absorption value. Glycyrrhizin is the only phytochemical that has an absorption value < 30% hence poorly absorbed in the intestine.

Caco2 permeability

If log Papp is > 0.90, it means that the compound expresses high Caco-2 permeability and is easily absorbed [21]. Rosmarinic acid had the lowest log Papp, so it has the lowest Caco2 permeability. Meanwhile, 6-shogaol had the highest log Papp. Moreover, except

for glycyrrhizin, withaferin A, alphitolic acid, and kalambroside A, all other compounds had log Papp > 0.90, hence they have high Caco2 permeability.

3.2.2. Distribution

Volume distribution (VDss)

VDss is the theoretical value that the total dose of a drug would require to be uniformly distributed to give the same concentration as in blood plasma. VDss is considered to be low, if log VDss< −0.15. VDss is considered to be high, if log VDss > 0.45 [21]. The results indicated that VDss of 6-Shogaol and kalambroside A is high. Meanwhile, glycyrrhizin, oleanic acid, mangiferonic acid and alphitolic acid have low VDss.

Blood brain barrier (BBB) permeability

It is essential to determine the ability of a compound to cross BBB as it aids in reducing side effects and toxicity if the compound's pharmacological activity is not present in the brain. If the log BB > 0.3, the compound can readily cross the BBB [22]. If the log BB < −1, the molecule poorly distributed to the brain [22]. The results indicate that Kalambroside A, Rosmarinic acid, Glycyrrhizin and fluticasone propionate cannot cross BBB. However, stigmasterol has log BBB > 0.3 so it can readily cross the BBB.

3.2.3. Metabolism

Cytochrome P450 is an important enzyme system, mainly found in the liver, for drug metabolism. It is important to determine whether the compounds are inhibitors of the two main CYP 450 enzymes, namely CYP2D6 and CYP3A4 to avoid drug-drug interactions [23]. None of the phytochemicals inhibited CYP2D6 and CYP3A4. But the control drug inhibited CYP3A4.

3.2.4. Excretion

Total clearance

The predicted results show that 6-Shogaol has the highest total clearance. Except for glycyrrhizin and Kalambroside A, all phytochemicals have higher total clearance than the control chemical drug.

3.2.5. Toxicity

AMES test

A widely used method to assess a compound's mutagenic potential using bacteria. A positive result indicates that the compound is mutagenic therefore it may act as a carcinogen [24]. The results indicate that none of the selected compounds are mutagenic.

Hepatotoxicity

A compound is classed as hepatotoxic if it had at least one physiological or pathological liver event which strongly disrupts the liver's normal function [14]. The results suggest that none of the selected compounds were hepatotoxic, except alphitolic acid and oleanic acid.

Oral Rat Acute Toxicity (LD_{50})

Mangiferonic acid had a higher LD_{50} value than the control drug, which denotes that even at a higher dosage, it is less toxic compared to chemically synthesized drugs. Hence, it has fewer side effects and is safe for use.

4. Conclusions

In conclusion, mangiferonic acid is the best phytochemical as it obeys Lipinski's and Verber's rules, has a good bioactivity score towards NR, high intestinal absorption, high Caco-2 permeability, non-inhibitor of CYP450 enzymes, non-mutagenic, non-hepatotoxic, and has high LD_{50}. Hence it can be considered a potential drug to treat asthma. Additionally, withaferin A and stigmasterol are also eligible to use as anti-asthmatic drugs.

Author Contributions:

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Conflicts of Interest: The authors declare no conflict of interest.

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