PHARMACOKINETICS AND PHARMACODYNAMICS PREDICTED PROFILES OF STRIGOLACTONES – BIOINFORMATICS APPROACHES

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Abstract. Strigolactones (SLs) are a class of plant hormones β-carotenoid-derived that are synthesized in the roots of plants. They govern plant growth, development, and interactions with the environment. The first SL was isolated in 1966. Their various functions make them viable agricultural targets, and understanding these molecules may assist with creating strategies to increase crop yields and sustainability. In recent years, there has been considerable interest in the potential applications of SLs in biomedicine, especially in cancer therapy, diabetes or inflammation. These complex roles are related to a significant structural diversity. So far, all biomedical literature data has been dedicated to the synthetic analogs of these phytohormones. The bioinformatic approach supports a better understanding of the complexity of SLs, leading to a better design of bioactive compounds. This study provides an efficient in silico approach to evaluate the pharmacokinetic, pharmacodynamic, and drug-like characteristics of both natural and synthetic SLs, delivering significant insight into their biomedical potential.

Key words: Drug research, phytochemistry, ligand, biological targets, in silico.

INTRODUCTION

Strigolactones (SLs) are a novel class of phytohormones pivotal in regulating various plant growth and developmental processes [14]. Initially recognized as signaling molecules capable of inducing the germination of particular parasite plants, additional research has revealed their critical role in coordinating plant-fungal symbiotic interactions, thus enabling nutrient intake from the soil. Concurrently, SLs exert an important endogenous influence, driving a variety of physiological processes [1, 47]. The term "strigolactones" is related to both their biological function, primarily the germination induction on Striga genus of parasitic plants, and their chemical structure, which is characterized by lactone rings. The discovery of

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SLs dates back to 1966 when they were extracted from cotton plants, particularly the roots [25, 38]. Natural SLs are divided into two fundamentally different groups: canonical and non-canonical. Canonical SLs have a conserved structure that is characterized by an ABC ring (tricyclic lactone part) connected to a D-ring (butenolide) via an enol-ether bridge [7, 32]. Non-canonical SLs are characterized by an absence of the normal ABC-rings but contain an enol-ether bridge and D-ring fragment that can be linked to numerous structures [1, 42]. The studies that focused on the SL's structure-activity relationship illustrated that the D-ring fragment and the enol-ether bridge are indispensable for its biological activities [44]. Carlactone and its oxidized metabolites, including carlactonic acid and methyl carlactonoate, act as precursors in the biosynthesis process of strigol-type and orobanchol-type SLs [28]. Given the difficulty of isolating natural SLs due to their limited distribution in root exudates, SL investigation has led to the development of synthetic analogs [9]. While these synthetic analogs may exhibit slightly diminished activity, they generally demonstrate superior stability compared to their natural equivalents [15]. Typical SLs analogs include: GR24, Nijmegen-1, EM1, T101, MP1, and CISA-1 (cyano-isoindole strigolactone analogue-1) [1, 6, 15, 13]. These analogs represent valuable instruments for improving our understanding of the critical role of SLs in plant biology [14].

However, over the past few years, certain studies [11, 18, 30, 31] have gathered data on the effects of SLs on human cells and their potential applications in medicine. For example, SLs analogs have been shown to have an impact on human cells and the uncovering of their biomedical potential is ongoing [11].

As a result, the purpose of this study is to advance our understanding of the therapeutic potential of SLs analogs such as GR24 or ST362, but also of its fluorescently labeled synthetic variant, CISA-1. We intend to pay attention to natural SLs falling into both canonical and non-canonical categories, strigol and carlactone and we used the bioinformatics methods to predict the drug-like, pharmacokinetics, and pharmacogenomics profiles of compounds [3, 4].

The aim of this article is to examine the chemical properties of natural and synthetic SLs and evaluate their therapeutic potential using drug-likeness criteria, along with absorption, distribution, metabolism, excretion, and toxicity (ADMET) considerations. Additionally, we will investigate the molecular mechanisms involved in pharmacodynamics and the primary biological targets of these compounds.

MATERIALS AND METHODS

For the purpose of evaluating the biomedical potential of SLs and obtaining diversified results that can be extrapolated on a larger scale, we decided to test both synthetic analogs that were previously investigated in the literature (GR24 and ST362), a fluorescent-labeled synthetic analog (CISA-1), and natural SLs (strigol

and carlactone), which were not previously included in this type of research. All web servers use SMILES as input structural data to analyze the molecules.

DRUG-LIKENESS ASSESSMENT

Despite the fact that SLs first appeared as a class of plant hormones derived from carotenoids, additional studies shifted their attention to discovering additional biological roles connected with these molecules. The mode of action in plants, together with their distinct chemical scaffold, has influenced their prospective biological use [11, 30]. SLs analogs have been outlined in the literature as potential compounds with anticancer, anti-inflammatory, neuro anti-inflammatory, and antiviral properties, as well as promising molecules for treating insulin resistance and type 2 diabetes [11, 18, 30, 31].

The concept of drug-likeness offers valuable guidelines for early-stage drug research [27]. Medicinal filters, or molecular filters, are strategies used in medicinal chemistry to efficiently design chemical libraries for high-throughput virtual screening and drug development [17]. When analyzing chemical compounds to reach new treatments, it is essential to evaluate the bioavailability score. This is highly significant in pharmacokinetics and indicates the drug's direct absorption [17, 40].

We used SwissADME [52] to assess the drug-likeness of SLs. This involved examining their compliance with Lipinski, Veber, Ghose, Muegge, and Egan medicinal filters, in addition to determining bioavailability scores. A high bioavailability score indicates that the molecule will be effectively absorbed when supplied orally [10].

PHARMACOKINETICS EVALUATION

Pharmacokinetics is the study of the dynamic movements of foreign substances (xenobiotics) throughout the body [26]. A powerful drug candidate should not only be effective towards the therapeutic target but also must demonstrate feasible ADMET features at therapeutic doses [45].

By utilizing admetSAR 2.0 [48] we explored important ADMET features of each SL, including absorption, distribution, metabolism, excretion, toxicity, and interactions with cytochrome P450 enzymes. The probability of a prediction is a major component of the model's output. It reflects the model's confidence in its predictions [41].

PHARMACODYNAMICS ANALYSIS

Pharmacodynamics is a crucial aspect of modern medication development, increasing the process effectiveness [29]. SLs are gaining significant attention in the

drug discovery field due to their distinctive properties and potential therapeutic applications [2]. Understanding the new biological properties of SLs is critical for different purposes [11]. In plants, they serve as endogenous and exogenous hormones as well [26, 34].

Understanding the biological targets of compounds like SLs can help with the identification of receptors for specific medical conditions but also predict their therapeutic effects through understanding their molecular interactions.

Molinspiration software [49] concluded molecular processes of SLs, including interactions with G protein-coupled receptors (GPCR), kinases, nuclear receptors, proteases, and enzymes. Additionally, the SuperPred database [50] facilitated the identification of common as well as individual pharmacological targets. Model accuracy refers to how highly the machine learning model's predictions coincide to the actual results and it is an indicator of the model's performance [12].

RESULTS AND DISCUSSION

DRUG-LIKENESS OF STRIGOLACTONES

In Table 1, we predicted the medicinal rules and the bioavailability score for natural and synthetic SLs, specifically GR24, ST362, CISA-1, strigol, and carlactone, using SwissADME [10].

Table 1

Predicted medicinal rules and bioactivity score of GR24, ST362, CISA-1, strigol, and carlactone

Strigolactone	Lipinski	Veber	Ghose	Muegge	Egan	Bioavailability score
GR24	yes; 0 violation	yes	yes	yes	yes	0.85
ST362	yes; 0 violation	yes	yes	yes	yes	0.56
CISA-1	yes; 0 violation	yes	yes	yes	yes	0.56
strigol	yes; 0 violation	yes	yes	yes	yes	0.56
carlactone	yes; 0 violation	yes	yes	yes	yes	0.55

According to SwissADME, all SLs exhibit potential medicinal characteristics, as they do not violate any rules or filters used for analysis. The fact that SLs match pharmaceutical filters has a positive effect on their safety profile. High bioavailability scores were obtained in all five cases. ST362, CISA-1, and strigol were each assigned a value of 0.56. Carlactone had the lowest value (0.55), and GR24 had the highest (0.85). No substantial changes were found between natural SLs and synthetic analogs.

PHARMACOKINETICS OF STRIGOLACTONES

In Table 2, we predicted 23 in silico ADMET properties of each SL using admetSAR2.0 tool [43]. The probability or the unit of the predicted values is marked after.

Generally, the results generated by admetSAR 2.0 show no substantial differences between synthetic analogs and natural SLs. As a consequence, all five SLs examined can be absorbed at the intestinal level by humans and penetrate the blood-brain barrier. Except for ST362, all other compounds can be absorbed into the body after oral administration. None of the strigolactones examined have carcinogenic potential; nonetheless, all but carlactone are likely to cause an allergic skin reaction. Regarding additional types of toxicity that should be analyzed before human administration of compounds, none of the examined SLs exhibit hepatotoxicity or respiratory system toxicity. Only synthetic analogs carry the potential to produce micronuclei production, a type of genomic toxicity. Concerning reproductive system toxicity, ST362, CISA-1, and strigol are the strigolactones that pose a risk, while at the mitochondrial level, all except carlactone do so. GR24, CISA-1, and carlactone are potential nephrotoxic compounds. Only strigol, the first isolated natural SL, is classified as Class I in acute oral toxicity, indicating the potential toxicity of a chemical compound when administered orally. The other four are classified as Class III.

According to admeSAR 2.0, all SLs have the potential to bind to the estrogen receptor, while only ST362 and strigol may bind to the androgen receptor. In silico action on the thyroid receptor was predicted for all SLs, except GR24, while action on the glucocorticoid receptor may occur only with ST362, CISA-1, and strigol. For the nuclear receptor PPAR gamma, GR24 is the only SL for which activity has not been predicted. Among synthetic analogs, binding activity to aromatase has been predicted only for CISA-1, while this type of binding has been calculated for both natural SLs. GR24, CISA-1, and strigol are the SLs with lower plasma binding percentages, indicating that they have the ability to perform biological action.

The synthetic analog GR24 exhibits substrate activity on CYP3A4 but not inhibitory activity. It acts as both a substrate and inhibitor for CYP2C19, while showing substrate activity for CYP2C9. Additionally, it demonstrates inhibitory activity on CYP1A2. It is neither an inhibitor nor a substrate for CYP2D6. ST362, another synthetic analog, exhibits dual activity as both a substrate and an inhibitor on CYP3A4. It is not a substrate for either CYP2C9 or CYP2D6. It also shows inhibitory activity on CYP2C9 and CYP1A2. The fluorescent-labeled synthetic analog, CISA-1, exhibits dual action on CYP3A4. No action has been predicted on either CYP2C19 or CYP2C9. Moreover, it is neither a substrate nor an inhibitor for CYP2D6; however, only inhibitory action has been predicted for CYP1A2. The two natural SLs studied, strigol, and carlactone, have equivalent pharmacogenomic profiles. They both work as substrates only on CYP3A4, with no other effects predicted on the other cytochromes under investigation.

Table 2

ADMET prediction for GR24, ST362, CISA-1, strigol, and carlactone

Predicted feature	GR24	ST362	CISA-1	strigol	carlactone
Human intestinal absorption	+/ 0.99	+/ 0.92	+/ 0.97	+/ 0.99	+/ 0.99
Brain blood barrier	+/ 0.60	+/ 0.70	+/ 0.70	+/ 0.85	+/ 0.75
Human oral bioavailability	+/ 0.52	–/ 0.50	+/ 0.61	+/ 0.55	+/ 0.52
CYP3A4 substrate	+/ 0.59	+/ 0.68	+/ 0.68	+/ 0.62	+/ 0.63
CYP3A4 inhibition	–/ 0.75	+/ 0.68	+/ 0.68	–/ 0.60	–/ 0.88
CYP2C19 inhibition	+/ 077	+/ 0.77	–/ 0.54	–/ 0.92	–/ 0.59
CYP2C9 substrate	+/ 0.61	–/ 0.79	–/ 0.80	–/ 0.80	–/ 0.80
CYP2C9 inhibition	+/ 0.66	+/ 0.65	–/ 0.52	–/ 0.70	–/ 0.77
CYP2D6 substrate	–/ 0.86	–/ 0.87	–/ 0.87	–/ 0.87	–/ 0.87
CYP2D6 inhibition	–/ 0.91	–/ 0.83	–/ 0.84	–/ 0.96	–/ 0.93
CYP1A2 inhibition	+/ 0.83	+/ 0.54	+/ 0.65	–/ 0.75	–/ 0.52
Carcinogenicity (binary)	–/ 0.88	–/ 0.99	–/0.90	–/ 0.93	–/ 0.88
Micronuclear	+/ 0.70	+/ 0.66	+/0.66	–/ 0.72	–/ 0.90
Hepatotoxicity	+/ 0.58	–/ 0.50	+/0.61	+/ 0.64	+/ 0.58
Skin sensitisation	–/ 0.53	–/ 0.83	–/ 0.83	–/ 0.77	+/ 0.54
Respiratory toxicity	+/ 0.73	+/ 0.78	+/ 0.68	+/ 0.65	+/ 0.58
Reproductive toxicity	–/ 0.52	+/ 0.92	+/ 0.68	+/ 0.82	–/ 0.73
Mitochondrial toxicity	+/ 0.75	+/ 0.78	+/ 0.82	+/ 0.88	–/ 0.55
Nephrotoxicity	+/ 0.47	–/ 0.86	+/ 0.64	–/ 0.60	+/ 0.74
Acute oral toxicity (c)	III/ 0.43	III/ 0.64	III/ 0.65	I/ 0.36	III/ 0.66
Estrogen receptor binding	+/ 0.74	+/ 0.80	+/ 0.63	+/ 0.83	+/ 0.83
Androgen receptor binding	–/ 0.56	+/ 0.78	–/ 0.49	+/ 0.54	–/ 0.50
Thyroid receptor binding	–/ 0.68	+/ 0.80	+/ 0.66	+/ 0.51	+/ 0.74
Glucocorticoid receptor binding	–/ 0.48	+/ 0.87	+/ 0.80	+/ 0.75	–/ 0.55
Aromatase binding	–/ 0.48	–/ 0.59	+/ 0.52	+/ 0.61	+/ 0.74
PPAR gamma	–/ 0.62	+/ 0.71	+/ 0.69	+/ 0.61	+/ 0.74
Plasma protein binding	0.717/ 100 %	1.031/ 100 %	0.839/ 100 %	0.841/ 100 %	1.06/ 100 %

PHARMACODYNAMICS OF STRIGOLACTONES

In Table 3, the prediction of the molecular mechanisms of SLs was carried out by Molinspiration software [8]. The bioactivity score represents a numerical value predicted by Molinspiration that reflects a molecule's likelihood of interacting with a given biological target. This score is calculated considering the molecule's physical and chemical attributes. The greater the bioactivity score, the more probable the chemical will interact with the target, thereby generating a biological reaction (Molinspiration Cheminformatics free web services, Slovensky Grob, Slovakia).

Table 3

Predicted molecular mechanisms for GR24, ST362, CISA-1, strigol, and carlactone.

Strigolactone	GPCR ligand (G protein-coupled receptors)	Ionic channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
GR24	0.48	0.10	0.06	0.28	0.08	0.40
ST362	0.15	–0.08	0.10	0.03	–0.25	0.03
CISA-1	0.19	0.01	–0.17	0.07	–0.09	0.08
strigol	0.36	0.06	–0.15	0.60	0.12	0.46
carlactone	0.05	0.04	–0.44	0.36	–0.21	0.31

Based on the results provided by Molinspiration, GR24, strigol, and carlactone show substantial molecular activity. Thus, GR24 can predominantly function as a ligand for GPCR, as well as for the nuclear receptor (0.48 and 0.28, respectively). It also received a high score for its enzymatic inhibitor function (0.40). Strigol shows the highest value in this analysis (0.60) for its ligand activity on the nuclear receptor. It also achieved values above the threshold for enzyme inhibition function (0.46), which is the highest in this category, as well as for its GPCR ligand activity. Carlactone is an SL that can be extremely effective as an enzyme inhibitor and nuclear receptor ligand, with estimated values higher than 0.30.

The evaluation of in silico molecular mechanisms has taken us closer to identifying the primary pharmacological targets for the SLs of interest, as these two features are inseparably linked when focusing on drug-like property testing. Furthermore, research dedicated to molecular targets contributes to understanding how these SLs may function in the human body.

We used the SuperPred database to identify the main pharmacological targets [51] of GR24, ST362, CISA-1, strigol and carlactone [12].

In Table 4 we grouped the common pharmacological targets for all five analyzed SLs, while in Table 5, we mentioned the unique targets.

Table 4

Common pharmacological targets for GR24, ST362, CISA-1, strigol, and carlactone

Target	UniProt ID	Strigolactone	(%) Probability	(%) Model accuracy
Transcription intermediary factor 1-alpha	O15164	GR24	94.86	95.56
		ST362	97.85	
		CISA-1	93.79	
		strigol	94.38	
		carlactone	95.75	
Cathepsin D	P07339	GR24	89.85	98.95
		ST362	97.73	
		CISA-1	93.17	
DNA-(apurinic or apyrimidinic site) lyase	P27695	GR24	89.32	91.11
		strigol	92.63	
DNA topoisomerase II alpha	P11388	ST362	94.48	89.00
		CISA-1	92.54	
Kruppel-like factor 5	Q13887	strigol	88.72	86.33
		carlactone	93.78	
Histone deacetylase 2	Q92769	strigol	88.30	94.75
		carlactone	97.69	

Table 5

Unique pharmacological targets for GR24, ST362, CISA-1, strigol, and carlactone

Target	UniProt ID	Strigolactone	Probability (%)	Model accuracy (%)
Monoamine oxidase B	P27338	GR24	90.20	92.51
Casein kinase II alpha/beta	P67870		85.79	99.23
Hypoxia-inducible factor 1 alpha	Q16665	ST362	98.42	85.14
EGLN1	Q9GZT9		97.89	93.40
Endoplasmic reticulum-associated amyloid-beta-binding protein	Q99714	CISA-1	98.22	70.16
Bile acid G protein-coupled receptor 1	Q8TDU6		92.74	93.65
Cannabinoid receptor CB2	P34972	strigol	88.77	97.25
Cyclooxygenase 2	P35354	carlactone	97.43	89.63

The output from SuperPRED demonstrates that the investigated SLs contain both common and specific targets. For decisive results, we filtered by the highest binding probability, considering, wherever possible, the accuracy of the model. Our choice for the last category ranged from 85 % to 99 %. The endoplasmic reticulum-associated amyloid-beta-binding protein is the only one with a model accuracy of only 70 %, but the binding probability exceeds 98 % for CISA-1. For instance, all five SLs shared a common target, hypoxia-inducible factor 1-alpha, with binding probability ranging from 93 % to 97 %. Cathepsin D was a common target only for three synthetic SL analogs, namely GR24, ST362, and CISA-1. ST362 had the highest binding probability to cathepsin D, slightly above 97 %. It can be

hypothesized that DNA-(apurinic or apyrimidinic site) lyase is not a specific target because it was identified in both synthetic SL (GR24) and natural ones (strigol, carlactone). Histone deacetylase 2 and Kruppel-like factor 5 are targets identified only in natural SLs, with a higher binding probability for carlactone in both cases.

SLs' common targets serve major functions, such as gene expression regulation [37], protein degradation [24], DNA structure and repair mechanisms [20, 21, 23], chromatin structure [46]. As a result, these compounds may disrupt these processes, affecting cell function and, ultimately, the organism. Based on this starting point, it is necessary to investigate if they may be used to treat disorders in which these mechanisms are abnormal, such as cancer [22].

In the case of unique targets, it can be postulated, for example, that these SLs may have therapeutic implications in neurodegenerative diseases, specifically Alzheimer's disease (such as GR24, which targets monoamine oxidase B involved in regulating levels of amyloid-beta in neurons [36], or CISA-1 which targets the endoplasmic reticulum-associated amyloid-beta-binding protein associated with Alzheimer's disease [5], a protein that binds to beta-amyloid, the main component of amyloid plaques in the brains of Alzheimer's patients. Strigol targets cannabinoid receptors involved in multiple processes, including inflammation [39], while carlactone targets COX-2 and its selective inhibitors can be utilized to alleviate inflammation [33]. ST362 targets HIF-1alpha and EGLN1 [16], both involved in cellular adaptation to low oxygen levels, which play a major role in cancer where hypoxia is known.

CONCLUSIONS

SLs are complex and dynamic molecules. Our study presents an accurate in silico analysis of the pharmacokinetic, pharmacodynamic, and drug-like features of both natural and synthetic SLs. By exploring their therapeutic potential, we aim to improve the knowledge of their medicinal applications. The drug-likeness evaluation revealed that all tested compounds showed potential medicinal characteristics. Synthetic analogs and natural compounds demonstrated similar compliance with pharmaceutical filters, underlining their safety profile. The pharmacokinetic evaluation showed that SLs can be absorbed at the intestinal level and penetrate the blood-brain barrier, with synthetic analogs and natural substances having similar profiles.

While all compounds had potential biological activity, only synthetic analogs induced micronuclei. GR24, strigol, and carlactone exhibited significant activity as GPCR and nuclear receptor ligands, as well as enzymatic inhibitors, based on molecular mechanism analysis. Moreover, we identified both common and unique pharmacological targets, which represent a starting point for the subsequent SL analysis in the context of certain medical conditions.

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