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In silico pharmacophore evaluation of some important medicinal plants of Chhattisgarh

ABSTRACT

Traditional Plants of Medicinal Importance (TPMI) are essential components of healthcare systems in developing countries. The WHO estimates that around 30% of plant species have been utilized for medicinal purposes. The pharmacological assessment of TPMI is complex and costly, encompassing extraction, compound identification, *in vitro* and *in vivo* validation, and data interpretation. This process is labor-intensive and frequently confines studies to in vitro evaluations, thereby constraining the potential for pharmaceutical drug development. Bioinformatics tools like SwissADME, PubChem, and ChemSpider provide effective solutions for large-scale screening of plant bioactive compounds. *Embelia ribes* and *Gloriosa superba*, two rare indigenous plants, have been selected for *in silico* pharmacophore evaluation during the present course of investigation. We have highlighted the immense potential of *E. ribes* and *G. superba*, underscoring their rich repertoire of bioactive compounds, including caffeic acid, chlorogenic acid, cinnamic acid, o-cumaric acid, embelin, vanillic acid, colchicine, and colchicoside. The identification of key biological targets including MMP-9, HCAR2, SLC22A3, and ALOX5 for these bioactive compounds emphasizes their relevance in treating conditions such as papillary thyroid cancer and inflammatory diseases. Additionally, the favorable physicochemical properties, such as low tPSA values, suggest promising bioavailability and absorption, further supporting their potential as viable drug candidates. The pharmacophore assessment conducted in this study reflects the increasing significance of computational tools in expanding the frontiers of drug discovery from traditional medicinal plants.

Keywords: Bioactive compounds, Embelia ribes, Gloriosa superba, SwissADME, in silico pharmacophore, MMP-9, HCAR2, SLC22A3, ALOX5

INTRODUCTION

Populations of Developing countries depend on Traditional Plants of Medicinal Importance (TPMI) for their day-to-day health care needs. World Health Organization (WHO) reported that around 30% of plant species have once been used for medicinal purposes (Schippmann et al., 2002). The identification and prediction of the pharmacological potential of TPMI is a sophisticated chore due to a bunch of experimental setups and high-end modern analysis expenses. The traditional approach for medicinal plant research was done under the following phases; (a) the extraction of a bioactive compound of interest in pure form, (b) qualitative and quantitative identification of extracted bioactive compound (c) screening for *in vitro* pharmacological efficacy (d) validation of *in vivo* pharmacological efficacy in an animal models (e) data collection and significant interpretation (Zhang et al., 2017; Yi et al., 2016). As seen above, the traditional research approaches are prolonged and expensive. The TPMI comprises numerous bioactive compounds but due to the expensiveness of traditional tactics screening and development of pharmaceutical drugs from medicinal plants demands higher cost and time consumption. Thus, the most of literature has limited their research to *in vitro* pharmaceutical potential rather than *in vivo* pharmaceutical draggability screening. To overcome such limitations, bioinformatics tools are promising due to the availability of a vast and comprehensive biological database of plant-derived bioactive compounds. A variety of bioinformatics tools are accessible for the *in-silico* study of phytochemicals and their application e.g., zinc docking tool, SwissADME, ChEMBL, PubChem, ChemSpider, UniChem and so forth. These tools are significantly used for the large-scale screening of plant-derived bioactive compounds for systematic evaluation of their pharmaceutical potential and target cells or biological components. The advancement of computer and information technology pushes the use of an *in-silico* method for the search for novel plant-derived bioactive compounds for screening draggability and development of drugs using Computer-Aided Drug (CAD) design. The *in-silico* approaches help to predict the possible interaction between simulated compounds and biological targets accurately.

The expansion of the pharmacology database helps toward the rapid and wide-ranging elucidation of the relationships between plant-derived bioactive compound and their targets& overall regulatory mechanism (i.e., Protein-Ligand interaction) (Rubio-Perez et al., 2015; Zhang et al., 2016). The network analysis under systems biology is used to predict the numerous characteristics of signal nodes (i.e., plant-derived bioactive compounds) for multiple targets with special reference to draggability. Hence, with such a bioinformatics facility, researchers can explore the chemical composition and pharmacological potential of traditional medicine. The present work was focused on the study of traditional plants of medicinal importance to human health practices. A total of 11538.64 ha is occupied by medicinal & aromatic plant cultivation in Chhattisgarh state as per the Agri-portal database reflected on

Horticulture Department, Government of Chhattisgarh. Thereby, the Chhattisgarh state offers tremendous opportunities to screen *in-silico* pharmacophore assessment of indigenous medicinal flora. In-line, two medicinal plants viz., *Embelia ribes* and *Gloriosa superba* have been selected as rare indigenous medicinal flora of Chhattisgarh and processed for the preliminary *in-silico* pharmacophore evaluation. Choudhary et al. (2021) reviewed the pharmacology importance of the phenolic content of *Embelia ribes* for pharmaceutical importance. Haq et al., (2005) evaluated fresh berries of *E. ribes* and claimed that they consisted of caffeic acid, chlorogenic acid, cinnamic acid, o-cumaric acid, and vanillic acid. Novel bioactive agents embelin (ver., embelinol, and embeliol) have also been reported in fresh berries of *E. ribes* (Indrayan et al., 2005). Jasmine *et al.* (2020) reported that the Colchicine and Colchicoside found in *Gloriosa superba* L as secondary metabolites. Chopra et al. (1956) and Sarin et al. (1977) revealed that the *Colchicum luteum* and *Gloriosa superba* consisted of colchicines at a range of 0.62 to 0.9%. Later, Srivastava et al. (1977) and Bellet and Gaignault (1985) claimed that the *G. superb* has been observed to have more colchicine than *Colchicum luteum*. Hence, the TPMI viz., *E. ribes* and *G. superba* were evaluated for their *in-silico* Pharmacophore efficacy. The aforementioned pieces of literature revealed that caffeic acid, chlorogenic acid, cinnamic acid, o-cumaric acid, colchicine, embelin, and vanillic acid have significantly contributed to the medicinal potency of *E. ribes* and *G. superba*. Thus, the present course of the investigation was carried out to document the *in silico* pharmacophore profile of caffeic acid, chlorogenic acid, cinnamic acid, o-cumaric acid, colchicine, embelin, and vanillic acid.

MATERIALS AND METHODS

The present research work was based on the gathering and analysis of the biological database of selected bioactive compounds that belong to *E. ribes* and *G. superba* using bioinformatics tools.

Selection of Bioactive Compounds

The bioactive compounds from medicinal plants (namely *E. ribes* and *G. superb*) viz., caffeic acid, chlorogenic acid, cinnamic acid, o-cumaric acid, colchicine, embelin, and vanillic acid have been selected for their pharmacophore analysis based on the literature survey.

Evaluation of pharmacological potential of TPMI

To meet the objective of the study the following approach was used to divulge the pharmacological potential of TPMI (viz., *E. ribes* and *G. superba*); (a) exploring the research significance of the TPMI, (b) searching, collection, and organization of biological database available online selected bioactive compounds, (c) prediction of pharmacophore efficacy of selected bioactive compounds and (d) ADME (absorption, distribution, metabolism, and excretion) analysis.

Zinc docking and SwissADME

The online zinc docking tool (https://zinc.docking.org/), ChemSpider (http://www.chemspider.com/) and SwissADME (http://www.swissadme.ch/) were used to predict the pharmacophore properties of selected bioactive compounds. The zinc docking tool was selected because it offers interoperability with the most reliable chemoinformatics tools i.e., ChEMBL (Bento et al., 2014), PubChem (Li et al., 2010), ChemSpider (RSC ChemSpider), and UniChem (Chambers et al., 2014; Chambers et al., 2013).

Lipinski's rule

Lipinski's rule of five assists in deciding the drug-likeliness of molecules based on the established rule related to molecular mass, lipophilicity, hydrogen bond donors and acceptor and molar refractivity range for pharmaceutical drug candidates (Lipinski, 2004; Jayaram et al., 2012). Lipinski's rule of five is mentioned in Table 1. The most probable target biological moiety was retrieved from the ChEMBL-20 database.

Table 1. Lipinski's rule of five

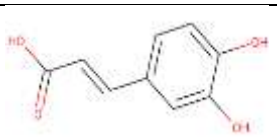
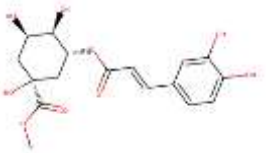
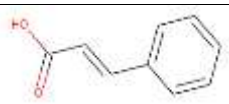
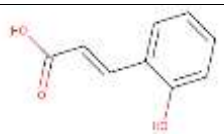
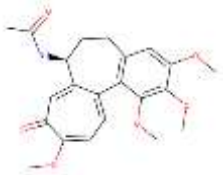
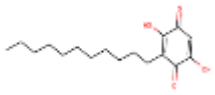
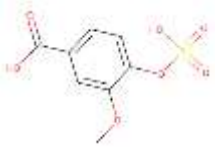
Molecular Weight (g/mol)	Lipophilicity (MLogP)	H-Bond Donors	H-bond acceptors	Rule Violation/ Molar Refractivity	Drug Likeness
<500	<5	<5	<10	<2 / 40-130	Yes
>500	>5	>5	>10	>2/ >40 and <130	No

RESULTS AND DISCUSSION

TPMI viz., *E. ribes* and *G. superb* were evaluated for pharmacophore analysis using a zinc docking tool. The bioactive compounds viz., Caffeic acid (ID- ZINC58172), Chlorogenic acid (ID-ZINC6482465), Cinnamic acid (ID- ZINC16051516), o-cumaric acid, Colchicine version COLCRYS (ID- ZINC621853), Embelin (ID- ZINC1531764), Vanillic acid (ID-

ZINC1644138) were screen for pharmacophore analysis. The molecular structure and SMILES (Simplified Molecular Input Line Entry System) file of these bioactive compounds is depicted in Table 2. The molecular weight, molecular formula, H-bond donor, H-bond acceptor, tPSA (total Polar Surface Area) and most probable target biological moiety were tabulated in Table 3.

Table 2. Molecular structure of selected bioactive compounds

S.N.	Bioactive Compound	Structure	SMILES
1.	Caffeic acid ZINC58172		O=C(O)/C=C/c1ccc(O)c(O)c1
2.	Chlorogenic acid ZINC6482465		COC(=O)[C@]1(O)C[C@@H](O)[C@@H](O)[C@H](OC(=O)/C=C/c2ccc(O)c(O)c2)C1
3.	Cinnamic acid ZINC16051516		O=C(O)/C=C/c1ccccc1
4.	o-cumaric acid (var. 2-Coumarate)		O=C(O)/C=C/c1ccccc1O
5.	Colchicine (COLCRYS) ZINC621853		COc1cc2c(c(OC)c1OC)-c1ccc(OC)c(=O)cc1[C@@H](NC(C)=O)CC2
6.	Embelin ZINC1531764		CCCCCCCCCCCC1=C(O)C(=O)C=C(O)C1=O
7.	Vanillic acid ZINC1644138		COc1cc(C(=O)O)ccc1OS(=O)(=O)O

NDA – No data available

The Caffeic acid, Cinnamic acid, Colchicine and Embelin were found as significant pharmacological draggability for MMP9_HUMAN (linked with papillary thyroid cancer), HCAR2, SLC22A3 and ALOX5. Prasanna and Doerksen (2009) mentioned that the tPSA (total Polar Surface Area) values below 140 Å indicated that good intestinal absorption is expected for the

new drug candidates. Similarly, these potent bioactive compounds have a maximum of 83 Å (Table 3)

Table 3. Zinc Database of selected bioactive compounds

S.N.	Bioactive Compound	Molecular weight	Molecular formula	tPSA	The most probable target as per the ChEMBL 20 database
1.	**Caffeic acid**	180.159	$C_9H_8O_4$	80	pKi (L.E.) - 8 MMP9_HUMAN
2.	**Chlorogenic acid**	368.338	$C_{17}H_{20}O_9$	153	There is no known activity for this compound.
3.	**Cinnamic acid**	148.161	$C_9H_8O_2$	40	pKi (L.E.) – 5.31 HCAR2
4.	**o-cumaric acid**	**NDA in ZINC database**			
5.	**Colchicine**	399.443	$C_{22}H_{25}NO_6$	83	pKi (L.E.) – 6.92 SLC22A3
6.	**Embelin**	294.391	$C_{17}H_{26}O_4$	74.60	pKi (L.E.) – 7.22 ALOX5
7.	**Vanillic acid**	248.212	$C_8H_8O_7S$	NDA	There is no known activity for this compound.

The mining of the Zinc Database for selected bioactive compounds viz., Caffeic acid, Chlorogenic acid, Cinnamic acid, o-cumaric acid, Colchicine, Embelin, and Vanillic acid, provided insights into their molecular properties and probable biological targets. The molecular weights of the compounds ranged from 148.161 g/mol (Cinnamic acid) to 399.443 g/mol (Colchicine). Their molecular formulas varied accordingly, with Caffeic acid ($C_9H_8O_4$) and Chlorogenic acid ($C_{17}H_{20}O_9$) being representative of structurally diverse groups. The topological polar surface area (tPSA) spanned from 40 (Cinnamic acid) to 153 (Chlorogenic acid), influencing their solubility and permeability.

Based on the ChEMBL 20 database, Caffeic acid exhibited probable activity against MMP9_HUMAN with a pKi (L.E.) value of 8, indicating strong target binding potential. Cinnamic acid showed a pKi (L.E.) of 5.31 for HCAR2, suggesting moderate activity. Colchicine demonstrated a pKi (L.E.) of 6.92 with SLC22A3, while Embelin had a pKi (L.E.) of 7.22 for ALOX5, indicating potential pharmacological relevance. However, Chlorogenic acid and Vanillic acid did not show any known activity in the database. Furthermore, o-Coumaric acid and Vanillic acid were marked as NDA (No Data Available) in the Zinc database, indicating a lack of documented interaction with known biological targets. Conclusively, the present research work revealed that Caffeic acid, Cinnamic acid, Colchicine, and Embelin had potential biological activity, whereas Chlorogenic acid and Vanillic acid

lacked recorded target interactions. The absence of data for o-Coumaric acid and Vanillic acid highlighted the need for further investigation into their bioactivity.

Rashid and Bardaweel (2023) stated that the MMPs belong to a family of zinc-dependent proteolytic metalloenzymes. MMP-9, a member of the gelatinase B family, is characterized as one of the most intricate MMPs. They also pointed the crucial involvement of MMP-9 in extracellular matrix (ECM) remodeling underscores its significant correlation with each stage of cancer pathogenesis and progression. Pan et al. (2023) documented that the HCAR2 belongs to the family of class A G protein-coupled receptors with key roles in regulating lipolysis and free fatty acid formation in humans. It is deeply involved in many pathophysiological processes and serves as an attractive target for the treatment of cardiovascular, neoplastic, autoimmune, neurodegenerative, inflammatory, and metabolic diseases. Nguyen et al. (2023) divulged that the SLC22A3 gene encodes the organic cation transporter (OCT)-3 and is associated with the prognosis of various cancer types. Nonetheless, its function in lung squamous cell carcinoma (LSCC) remains unexplored in other studies. Poirier et al. (2020) mentioned that the 5-lipoxygenase (5-LO), encoded by the ALOX5 gene, is expressed in leukocytes and facilitates the synthesis of leukotrienes, which are pro-inflammatory lipid mediators. Leukotrienes play a crucial role in immune responses and are implicated in inflammatory disorders, with 5-LO expression linked to the persistence of leukaemia stem cells. Understanding the biological processes that regulate 5-LO expression is essential. Additionally, they examined the regulation of 5-LO expressing themselves and leukotriene production during the maturation process of human monocytic cells.

Table 4. Pharmacokinetics (ADME) prediction of selected bioactive compounds

Bioactive Compound	**Caffeic acid**	**Chlorogenic acid**	**Cinnamic acid**	**o-cumaric acid (Chemspider databse)**	**Colchicine**	**Embelin**	**Vanillic Acid**
Formula	$C_9H_8O_4$	$C_{17}H_{20}O_9$	$C_9H_8O_2$	$C_9H_8O_3$	$C_{22}H_{25}NO_6$	$C_{17}H_{26}O_4$	$C_8H_8O_7S$
Molecular Weight (g/mol)	**180.16**	**368.34**	**148.16**	**164.16**	**399.44**	**294.39**	**248.21**
H-Bond Acceptors	**4**	**9**	**2**	**3**	**6**	**4**	**7**
H-Bond Donor	**3**	**5**	**1**	**2**	**1**	**2**	**2**
Molar Refractivity (40-130)	**47.16**	**87.82**	**43.11**	**45.13**	**109.36**	**84.31**	**52.11**
TPSA (A2)	**77.76**	**153.75**	**37.30**	**57.53**	**83.09**	**74.60**	**118.51**
Average Lipophilicity (LogPo/w)	**0.93**	**-0.00**	**1.79**	**1.40**	**2.36**	**3.68**	**0.39**
Water Solubility (LogS, ESOL)	**Soluble (-1.89)**	**Soluble (-1.84)**	**Soluble (-2.37)**	**Soluble (-2.37)**	**Soluble (-2.90)**	**-4.42**	**-1.83**
Pharmacokinetics (GI absorption)	**High**	**Low**	**High**	**High**	**High**	**Moderately soluble**	**High**
DrugLikeness (Lipinski)	**Yes, 0 violation**	**Yes, 0 violation**	**Yes;**	**Yes; 0 violation**	**Yes; 0 violation**	**Yes,**	**Yes;**

			0 violation			0 violation	0 violation
Bioavailability Score	0.56	0.55	0.85	0.85	0.55	0.85	0.56
Synthetic accessibility	1.81 (Very easy)	4.27 (Moderate)	1.67	1.85	3.87	3.66	2.25
Leadlikeness	No; 1 violation: MW<250	No; 1 violation: MW>350	No; 1 violation: MW<25	No; 1 violation: MW<250	No; 1 violation: MW>350	No; 2 violations	No; 1 violation

The present study analyzed seven bioactive compounds—Caffeic acid, Chlorogenic acid, Cinnamic acid, o-Coumaric acid, Colchicine, Embelin, and Vanillic acid—based on their molecular characteristics, pharmacokinetics, and drug-likeness. Their molecular weights ranged from 148.16 g/mol for Cinnamic acid to 399.44 g/mol for Colchicine. The hydrogen bond acceptors varied between 2 (Cinnamic acid) and 9 (Chlorogenic acid), while the number of hydrogen bond donors ranged from 1 (Cinnamic acid, Colchicine) to 5 (Chlorogenic acid). Molar refractivity values fell between 43.11 (Cinnamic acid) and 109.36 (Colchicine), indicating differences in molecular size and electronic distribution. The lipophilicity (LogP) values demonstrated a wide range, with Chlorogenic acid having the lowest (-0.00) and Embelin the highest (3.68). Most of the compounds exhibited good water solubility, except for Embelin, which had a LogS value of -4.42, indicating poor solubility. Regarding pharmacokinetics, most compounds showed high gastrointestinal (GI) absorption, except for Chlorogenic acid, which exhibited low absorption, and Embelin, which was moderately absorbed.

In terms of drug-likeness, all compounds complied with Lipinski's Rule of Five, suggesting their potential as drug candidates. The bioavailability scores varied, with Cinnamic acid, o-Coumaric acid, and Embelin achieving the highest score of 0.85, while the others ranged between 0.55 and 0.56. However, none of the compounds fully met lead-likeness criteria due to molecular weight constraints or other structural limitations. Synthetic accessibility scores indicated that Cinnamic acid (1.67) and Caffeic acid (1.81) were the easiest to synthesize, whereas Chlorogenic acid (4.27), Colchicine (3.87), and Embelin (3.66) presented moderate synthetic difficulty. Overall, these bioactive compounds exhibited diverse pharmacokinetic and physicochemical properties. Most of them were highly soluble, drug-like, and bioavailable, though Chlorogenic acid showed poor GI absorption and Embelin displayed low solubility, which could impact their pharmacological applications.

CONCLUSION

The investigation of TPMI is essential for identifying new treatments, especially in underdeveloped nations where traditional medicine is integral to healthcare. The amalgamation of bioinformatics and in silico techniques has transformed the pharmacological evaluation of

TPMI, markedly diminishing the time and expense limitations inherent in traditional experimental methods. We have emphasised the significant potential of medicinal plants like *E. ribes* and *G. superba* by highlighting their extensive array of bioactive chemicals. The identification of critical biological targets such as MMP-9, HCAR2, SLC22A3, and ALOX5 for these bioactive chemicals underscores their significance in the treatment of disorders like papillary thyroid carcinoma and inflammatory diseases. The advantageous physicochemical characteristics, including low tPSA values, indicate promising bioavailability and absorption, hence reinforcing their potential as viable therapeutic candidates. This integrated approach corresponds with current endeavours to reconcile old knowledge with contemporary medication development, promoting sustainable and creative healthcare solutions.

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