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# ADMET Prediction Compounds of Polar Extract Curcuma rhizoma

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***Abstract***

The pharmacokinetic and metabolic profiles of polar extract compounds from Curcuma rhizoma were evaluated using ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) predictions. Most compounds exhibited high gastrointestinal (GI) absorption, with the exception of D-glucose, citric acid, and terpenoids such as alpha-pinene and zingiberene, which demonstrated low absorption, highlighting potential challenges for systemic bioavailability. Blood-brain barrier (BBB) permeability was observed in lipophilic compounds like xanthorrhizol, bisdemethoxycurcumin, and terpenoids, suggesting their potential for CNS-targeted therapies, while polar compounds, including D-glucose, citric acid, and most curcuminoids, were non-permeant. D-glucose was the only compound identified as a P-glycoprotein (Pgp) substrate, indicating minimal efflux-related limitations for other compounds. Selective cytochrome P450 (CYP) enzyme inhibition was detected in compounds such as xanthorrhizol, curcuminoids, and zingiberene, suggesting potential metabolic interactions in multi-drug contexts. Promising therapeutic candidates include curcuminoids and xanthorrhizol, while non-BBB-permeant and low-absorbing compounds may require formulation strategies or alternative applications. These findings provide valuable insights into the pharmacological optimization of Curcuma rhizoma compounds, offering a foundation for further research in drug discovery and development.

***Keywords:*** ADMET prediction; *Curcuma rhizoma*; pharmacokinetics; gastrointestinal absorption; blood-brain barrier (BBB) permeability; cytochrome P450 inhibition; drug discovery.

## INTRODUCTION

Natural products derived from medicinal plants have long been a vital source of bioactive compounds in drug discovery and development [1]. Among these, the rhizome of *Curcuma xanthorrhiza* commonly known as Javanese turmeric has gained significant attention due to its diverse pharmacological properties, including anti-inflammatory, antimicrobial, and antioxidant activities [2]-[4]. The polar extract of Curcuma rhizome contains a range of secondary metabolites, such as terpenoids and phenolics, which are believed to contribute to its medicinal efficacy [5], [6].

The drug development process involves several stages, with absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling being a critical step in evaluating a compound's potential for therapeutic use [7], [8]. Computational tools, such as ADMET predictors, have emerged as efficient alternatives to experimental methods, offering rapid and cost-effective insights into the pharmacokinetic and toxicological properties of natural compounds [9], [10]. These tools provide crucial information on drug-likeness, bioavailability, and safety, enabling researchers to prioritize compounds for further investigation [11].

This study aims to predict the ADMET properties of compounds found in the polar extract of Curcuma rhizome using advanced computational methods. By focusing on in silico approaches, this

research seeks to identify potential drug candidates from the extract, contributing to the broader understanding of Curcuma as a source of novel therapeutic agents.

## RESEARCH METHOD

### Collecting Data

Chemical compounds derived from publications were gathered in two-dimensional sdf format via the database PubChem (https://pubchem.ncbi.nlm.nih.gov/).

### ADMET Prediction

Each acquired chemical compound structure is transformed into the Simplified Molecular Input Line Entry System (SMILES) format. Forecasting absorption, distribution, metabolism, excretion, and toxicity (ADMET) property attributes with the SWISSADME online application (http://www.swissadme.ch/) [12].

## RESULT AND DISCUSSION

The data analysis revealed the presence of various organic compounds, namely D-glucosa, citric acid, malic acid, lactic acid, xanthorrhizol, curcumin, demothoxycurcumin, bisdemothoxycurcumin, alpha pinene, alpha thujene, beta pinene, myrcene, linalool, zingiberene (**Tabel 1**), including carbohydrates, acids, terpenoids, and phenolic compounds. These findings highlight the chemical diversity within the sample, which could contribute to its potential applications in various fields, such as pharmacology, food industry, and cosmetics [13], [14].

**Table 1**. Natural compound properties of Curcuma xanthorriza rhizoma with ADMET prediction

| Compounds | Formula | GI absorption | BBB permeant | Pgp substrate | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|---|---|---|---|---|---|---|---|---|---|
| D-glucosa | $C_6H_{12}O_6$ | Low | No | Yes | No | No | No | No | No |
| Citric acid | $C_6H_8O_7$ | Low | No | No | No | No | No | No | No |
| Malic acid | $C_4H_6O_5$ | High | No | No | No | No | No | No | No |
| Lactic acid | $C_3H_6O_3$ | High | No | No | No | No | No | No | No |
| xanthorrhizol | $C_{15}H_{22}O$ | High | Yes | No | No | No | Yes | Yes | No |
| Curcumin | $C_{21}H_{20}O_6$ | High | No | No | No | No | Yes | No | Yes |
| Demothoxycurcumin | $C_{20}H_{18}O_5$ | High | No | No | Yes | No | Yes | No | Yes |
| bisdemothoxycurcumin | $C_{19}H_{16}O_4$ | High | Yes | No | Yes | No | Yes | No | Yes |
| Alpha Pinene | $C_{10}H_{16}$ | Low | Yes | No | No | No | Yes | No | No |
| Alpha thujene | $C_{10}H_{16}$ | Low | Yes | No | No | No | No | No | No |
| Beta Pinene | $C_{10}H_{16}$ | Low | Yes | No | No | No | Yes | No | No |
| Myrcene | $C_{10}H_{16}$ | Low | Yes | No | No | No | No | No | No |
| Linalool | $C_{10}H_{18}O$ | High | Yes | No | No | No | No | No | No |
| Zingiberene | $C_{15}H_{24}$ | Low | No | No | No | Yes | Yes | No | No |

Note: BBB: Blood-Brain Barrier; Pgp: P-glycoprotein

D-glucose ($C_6H_{12}O_6$), a simple carbohydrate, was identified as a major compound. Its presence suggests the sample could serve as a readily available energy source, making it applicable in nutritional formulations. Additionally, citric acid ($C_6H_8O_7$), malic acid ($C_4H_6O_5$), and lactic acid ($C_3H_6O_3$) were detected. These acids are widely recognized for their role as natural preservatives, pH regulators, and flavor enhancers. Citric acid, for example, is extensively used in the food and beverage industry due to its antioxidant properties and ability to chelate metal ions [15], thereby prolonging shelf life. Malic acid and lactic acid further enhance the potential utility of the sample in health-related applications, particularly in formulations aimed at improving gut health and metabolic processes [16].

Curcuminoids, including curcumin ($C_{21}H_{20}O6$), demethoxycurcumin ($C_{20}H_{18}O_5$), and bis dimethoxy curcumin ($C_{19}H_{16}O_4$), were among the most significant phenolic compounds identified. Curcuminoids are known for their strong antioxidant, anti-inflammatory, and anticancer properties. The high molecular complexity of these compounds underscores their potential as bioactive agents. Moreover, xanthorrhizol ($C_{15}H_{22}O$), another phenolic compound detected, has been reported to exhibit antimicrobial, antifungal, and anti-inflammatory activities [17]- [19]. These findings position the sample as a promising candidate for therapeutic and pharmaceutical development.

A variety of terpenoids were identified, including alpha-pinene ($C_{10}H_{16}$), beta-pinene ($C_{10}H_{16}$), alpha-thujene ($C_{10}H_{16}$), myrcene ($C_{10}H_{16}$), linalool ($C_{10}H_{18}O$), and zingiberene ($C_{15}H_{24}$). These compounds are widely recognized for their aromatic properties, which make them suitable for use in the fragrance industry [20]. Furthermore, terpenoids like linalool and alpha-pinene have demonstrated antimicrobial and anti-inflammatory properties, increasing their value for medicinal applications. Zingiberene, a sesquiterpene, is particularly noteworthy for its role in imparting the characteristic aroma of ginger and its reported potential in modulating immune responses [21].

The presence of a diverse array of compounds, including simple sugars, organic acids, phenolics, and terpenoids, suggests that the sample has broad-spectrum applicability. The high abundance of bioactive compounds, such as curcuminoids and terpenoids, indicates potential as a natural source of antioxidants and antimicrobials. This chemical diversity not only enhances its pharmacological value but also suggests potential for use as a multi-functional ingredient in food, cosmetics, and therapeutic formulations.

Further studies are recommended to quantify the identified compounds and investigate their synergistic effects. Bioassays should be conducted to evaluate the antioxidant, antimicrobial, and anti-inflammatory activities of the sample in vitro and in vivo. Additionally, exploring the stability and bioavailability of these compounds in complex matrices will help unlock their full potential in various applications. The findings provide a comprehensive chemical profile of the sample, offering a foundation for future research and industrial applications.

**Gastrointestinal Absorption**

The data presents an overview of the GI absorption properties of various compounds, highlighting their potential bioavailability upon oral administration. GI absorption is a critical factor influencing the pharmacokinetics and therapeutic efficacy of compounds [22].

Several compounds in this study, including D-glucose, citric acid, alpha-pinene, beta-pinene, alpha-thujene, myrcene, and zingiberene, exhibit low GI absorption. This suggests that these compounds may face barriers such as poor solubility, limited permeability, or rapid metabolism in the gastrointestinal tract. These findings could guide further formulation efforts, such as encapsulation or chemical modifications, to enhance their bioavailability.

Compounds such as malic acid, lactic acid, xanthorrhizol, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and linalool demonstrate high GI absorption. These compounds likely possess favorable physicochemical properties, such as optimal lipophilicity and molecular size, enabling efficient permeation across the intestinal epithelium. This high absorption potential may make these compounds more suitable for therapeutic applications without the need for extensive formulation adjustments [23].

The curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) uniformly exhibit high GI absorption. This finding aligns with existing literature suggesting that curcuminoids are relatively well-absorbed despite their limited systemic bioavailability due to rapid metabolism and clearance. These results reinforce the therapeutic potential of curcuminoids while emphasizing the importance of co-administration strategies (e.g., with piperine) to improve systemic exposure.

The terpenoids (alpha-pinene, beta-pinene, alpha-thujene, and zingiberene) show low GI absorption, which is consistent with their typically hydrophobic nature and potential degradation in the gastrointestinal environment. These properties highlight the need for delivery strategies, such as nanoemulsion systems, to improve their bioavailability and therapeutic efficacy.

The compounds with high GI absorption could be prioritized for further pharmacokinetic studies and clinical trials, as they are more likely to exhibit systemic therapeutic effects after oral administration. Conversely, low-absorbing compounds may be candidates for localized gastrointestinal applications or may require advanced delivery systems to overcome absorption challenges [24].

**BBB Permeant**

The blood-brain barrier (BBB) serves as a selective barrier that limits the entry of most compounds into the central nervous system (CNS) [25]. The BBB permeability data for the given compounds offers valuable insights into their potential to exert pharmacological effects on the brain or CNS.

Several compounds in the dataset, including D-glucose, citric acid, malic acid, lactic acid, curcumin, demethoxycurcumin, and zingiberene, are categorized as non-permeant to the blood-brain barrier (BBB). This lack of permeability can largely be attributed to their hydrophilic nature and polar functional groups, which hinder their ability to cross the lipophilic BBB. For example, organic acids like citric acid and malic acid possess charged carboxyl groups at physiological pH, reducing their likelihood of passive diffusion. The non-permeability of curcumin, a compound with significant therapeutic potential for neurodegenerative diseases, highlights the challenge of delivering hydrophilic molecules to the central nervous system (CNS) [26]. Such compounds may require structural modifications or advanced drug delivery techniques to enhance BBB penetration.

A subset of compounds, including xanthorrhizol, bisdemethoxycurcumin, alpha-pinene, alpha-thujene, beta-pinene, myrcene, and linalool, are identified as BBB permeant. These compounds share a common characteristic of high lipophilicity, which facilitates their passive diffusion across the lipid-rich barrier. Terpenoids like alpha-pinene, beta-pinene, and myrcene have been previously reported for their neuroprotective and anti-inflammatory properties, which align with their ability to cross the BBB. Similarly, linalool is well-known for its anxiolytic and sedative effects, possibly due to its CNS bioavailability [27]. The BBB permeability of xanthorrhizol and bisdemethoxycurcumin further supports their potential use in treating CNS disorders, such as neuroinflammation and oxidative stress-related conditions.

The dataset highlights an interesting contrast between curcumin and its structural derivative, bisdemethoxycurcumin. While curcumin is not BBB permeant, bisdemethoxycurcumin shows permeability, suggesting that subtle structural differences, such as the absence of methoxy groups, can significantly impact BBB penetration. This underscores the importance of molecular size and polarity in determining a compound's CNS accessibility. Another notable case is zingiberene, a lipophilic compound that unexpectedly lacks BBB permeability. This anomaly suggests that factors beyond lipophilicity, such as molecular size, stereochemistry, or interactions with specific transporters, may contribute to its limited CNS bioavailability.

**Pgp Substrats**

Among the 14 compounds analyzed, only D-glucose is identified as a Pgp substrate, consistent with its role in cellular metabolism and transport. The other compounds, including organic acids (citric, malic, and lactic acids), curcuminoids (curcumin and its derivatives), and terpenes (e.g., alpha-pinene, beta-pinene, and zingiberene), are not Pgp substrates. This indicates that their transport and pharmacokinetics are likely independent of Pgp-mediated efflux, with other factors like metabolism, solubility, or alternative transporters playing a more significant role.

The absence of Pgp interaction for most compounds has implications for bioavailability and therapeutic use. Non-substrate compounds may have improved absorption and reduced risk of Pgp-related drug-drug interactions [28]. This could enhance their efficacy, particularly in cases of Pgp-overexpression, such as multidrug-resistant cancers. Further research is recommended to investigate their alternative transport mechanisms, pharmacokinetics, and structure-activity relationships to optimize their therapeutic potential.

**CYP1A2 inhibitor**

Among the 14 compounds analyzed, only demethoxycurcumin and bisdemethoxycurcumin, derivatives of curcumin, are identified as inhibitors of the CYP1A2 enzyme. This enzyme plays a crucial role in the metabolism of various drugs and xenobiotics, and its inhibition can lead to altered pharmacokinetics of co-administered substrates [29]. The ability of these curcuminoids to inhibit CYP1A2 may contribute to their bioactivity, including potential interactions when used alongside drugs metabolized by this enzyme.

The remaining compounds, including D-glucose, organic acids (citric, malic, and lactic acid), terpenes (e.g., alpha-pinene, beta-pinene, and zingiberene), and other curcuminoids like curcumin itself, are not CYP1A2 inhibitors. This suggests they are less likely to interfere with CYP1A2-mediated drug metabolism, reducing the potential for drug-drug interactions. The findings highlight the importance of structural differences among curcuminoids in determining their enzymatic interactions and emphasize the need for further studies to understand their pharmacological implications and safety profiles.

**CYP2C19 inhibitor**

Among the 14 compounds analyzed, only zingiberene, a terpene commonly found in ginger, is identified as a CYP2C19 inhibitor. CYP2C19 is a key enzyme involved in the metabolism of various drugs, and its inhibition by zingiberene suggests a potential for drug interactions when co-administered with medications metabolized by this enzyme [30]. This highlights zingiberene's possible role in modulating drug metabolism, which could contribute to its pharmacological effects or pose risks depending on the therapeutic context.

The remaining compounds, including D-glucose, organic acids (citric, malic, and lactic acid), curcuminoids (curcumin and its derivatives), and other terpenes (alpha-pinene, beta-pinene, and linalool), are not CYP2C19 inhibitors. Their lack of interaction with this enzyme indicates a lower likelihood of CYP2C19-related drug-drug interactions. These findings suggest that zingiberene's unique inhibitory property warrants further investigation into its mechanism and potential applications in pharmacology or drug safety considerations.

**CYP2C9 inhibitor**

Several of the compounds analyzed, including xanthorrhizol, curcumin, demethoxycurcumin, bisdemethoxycurcumin, alpha-pinene, beta-pinene, and zingiberene, are identified as CYP2C9 inhibitors. CYP2C9 is a key enzyme responsible for metabolizing a wide range of drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants like warfarin [31]. The inhibition of CYP2C9 by these compounds suggests potential for significant drug interactions, which could alter drug efficacy or toxicity when these compounds are co-administered with CYP2C9 substrates. Notably, the curcuminoids and certain terpenes display strong inhibitory potential, indicating their structural relevance in modulating enzyme activity.

Conversely, D-glucose, citric acid, malic acid, lactic acid, alpha-thujene, myrcene, and linalool do not inhibit CYP2C9. These compounds are less likely to interfere with CYP2C9-mediated drug metabolism, reducing their risk for causing drug-drug interactions involving this enzyme. These findings highlight the importance of considering both the inhibitory potential and the structural properties of compounds during pharmacological and toxicological evaluations, especially for those with known CYP2C9 interactions. Further studies are recommended to determine the extent and clinical significance of CYP2C9 inhibition by these bioactive compounds.

**CYP2D6 inhibitor**

Among the compounds analyzed, only xanthorrhizol is identified as an inhibitor of CYP2D6, a critical enzyme involved in the metabolism of numerous drugs, including antidepressants, beta-blockers, and opioids. The inhibition of CYP2D6 by xanthorrhizol suggests a potential for drug-drug interactions when co-administered with medications metabolized by this enzyme. This interaction may affect the pharmacokinetics and therapeutic efficacy of such drugs, warranting caution in their concurrent use. The remaining compounds, including D-glucose, organic acids (citric, malic, and lactic acids), curcuminoids (curcumin and its derivatives), and terpenes (alpha-pinene, beta-pinene, linalool, and zingiberene), do not inhibit CYP2D6. This indicates a low risk of CYP2D6-related interactions for these compounds, making them safer options for co-administration with drugs reliant on CYP2D6 for metabolism. These findings highlight xanthorrhizol's distinct enzymatic interaction, suggesting the need for further investigation into its pharmacological implications and potential applications in modulating drug metabolism.

**CYP3A4 inhibitor**

The analysis reveals that curcumin, demethoxycurcumin, and bisdemethoxycurcumin are inhibitors of CYP3A4, an enzyme responsible for metabolizing a significant proportion of drugs, including steroids, immunosuppressants, and antineoplastic agents [32]. Inhibition of CYP3A4 by these curcuminoids indicates their potential to alter drug metabolism, possibly increasing the plasma concentrations of co-administered drugs metabolized by this enzyme. This interaction highlights the importance of monitoring and adjusting drug dosages when curcuminoids are used, particularly in therapeutic or dietary contexts.

The remaining compounds, including D-glucose, organic acids (citric, malic, and lactic acids), and terpenes (e.g., alpha-pinene, beta-pinene, linalool, and zingiberene), do not inhibit CYP3A4. Their

lack of interaction suggests they are less likely to interfere with CYP3A4-mediated drug metabolism, reducing the risk of drug-drug interactions. These findings emphasize the distinct inhibitory activity of curcuminoids on CYP3A4 and suggest further research is needed to explore their pharmacological effects and implications for drug safety.

## CONCLUSION

This study evaluates the pharmacokinetic and metabolic profiles of various compounds, revealing distinct characteristics relevant to drug discovery. Most compounds demonstrate high gastrointestinal (GI) absorption, except for D-glucose, citric acid, and terpenoids like alpha-pinene and zingiberene, which show low absorption, indicating potential challenges for systemic bioavailability. Several lipophilic compounds, including xanthorrhizol, bisdemethoxycurcumin, and terpenoids, exhibit blood-brain barrier (BBB) permeability, suggesting potential for CNS-targeted therapies, whereas polar compounds like D-glucose, citric acid, and most curcuminoids are not BBB permeant. P-glycoprotein (Pgp) substrate status is limited to D-glucose, implying reduced efflux-related limitations for the other compounds. Selective inhibition of cytochrome P450 (CYP) enzymes is observed in compounds such as xanthorrhizol, curcuminoids, and zingiberene, which may influence drug metabolism and necessitate caution in polypharmacy. Compounds with favorable profiles, such as curcuminoids and xanthorrhizol, exhibit promising therapeutic potential, while non-BBB-permeant and low-absorbing compounds may require formulation enhancements or be better suited for peripheral applications. These findings provide valuable insights into the optimization of these compounds for targeted therapeutic applications.

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