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COMPARATIVE ANALYSIS OF ONLINE DRUG–DRUG INTERACTION CHECKERS FOR ACCURACY, COMPLETENESS, AND CONSISTENCY

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ABSTRACT

Introduction: Drug–drug interactions (DDIs) are a major cause of preventable adverse drug reactions (ADRs), contributing to nearly one-quarter of ADR-related hospitalizations worldwide. With the increasing prevalence of polypharmacy, particularly among elderly and chronically ill patients, the risk of clinically significant DDIs has risen substantially. Subscription-based drug interaction databases such as Lexidrug™ are considered reliable because of their comprehensive, evidence-based information. However, in resource-limited settings, clinicians frequently rely on freely available online checkers like Medscape, Drugs.com, and DrugBank. Concerns remain regarding the accuracy, completeness, and consistency of these free tools.

Materials and methods: A cross-sectional study was conducted at the Institute of Pharmacology, Madras Medical College, Chennai, during August–September 2025. Using *Stockley's Drug Interactions* (11th edition), 150 drug pairs (140 interacting, 10 non-interacting) involving at least one cardiovascular agent were evaluated. Each pair was entered into Medscape, Drugs.com, and DrugBank, and results were compared with Lexidrug™ as the reference standard. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Completeness was scored on a 4-point scale (mechanism, severity, management, references), and agreement in severity grading was analyzed using Cohen's kappa.

Results: Drugs.com and DrugBank showed high sensitivity (>90%), while Medscape demonstrated lower sensitivity (~78%). Specificity was low across all platforms (≤40%), raising concerns about false positives and alert fatigue. Drugs.com provided the most comprehensive details, whereas DrugBank lacked clinical management advice. Agreement with Lexidrug™ severity grading was only fair ($\kappa = 0.23–0.38$).

Conclusion: Free DDI checkers offer accessible alternatives but show variable accuracy and completeness. Drugs.com performed best among free tools, though none matched the reliability of Lexidrug™. Regular validation and harmonization are needed to enhance their clinical utility.

Keywords: Drug–drug interactions, Lexidrug™, Medscape, Drugs.com, DrugBank, sensitivity.

INTRODUCTION

Drug-drug interactions (DDIs) manifest when the pharmacological efficacy of one medication is modified by the simultaneous administration of another, potentially amplifying or reducing therapeutic results, and in certain instances, leading to detrimental adverse drug reactions (ADRs). On a global scale, drug-drug interactions are acknowledged as a major factor in preventable morbidity and mortality, responsible for as much as one quarter of hospital admissions related to adverse drug reactions (1). As polypharmacy becomes increasingly common, characterized by the simultaneous administration of five or more medications, the likelihood of clinically significant drug-drug interactions has risen markedly. Individuals in advanced age and those suffering from chronic ailments, notably cardiovascular conditions, exhibit heightened susceptibility (2, 3). Cardiovascular agents, including anticoagulants, antiplatelets, and antiarrhythmics, are often associated with significant clinical considerations due to their narrow therapeutic indices and the elevated frequency of their prescription (4).

Clinical decision support systems (CDSS) and drug interaction checkers have become significant instruments for aiding prescribers in identifying potential drug-drug interactions (DDIs) at the point of care. These platforms are designed to offer extensive information, encompassing severity classification, mechanistic insights, and clinical management approaches (5). Among subscription-based resources, Lexidrug™ (Lexicomp), Micromedex, and Stockley's Drug Interactions are esteemed as reliable standards, bolstered by consistent updates and a foundation of evidence-based curation (6). Nonetheless, the financial constraints associated with these resources hinder accessibility in numerous low- and middle-income nations, thereby fostering a dependence on freely accessible alternatives (7).

Numerous free online drug interaction checkers, including Medscape, Drugs.com, and DrugBank, are extensively utilized owing to their accessibility and intuitive design (8-10). Medscape incorporates interaction checks within its clinical reference platform, Drugs.com presents a thorough interaction checker designed for both clinicians and patients, whereas DrugBank delivers pharmacological and biochemical insights in conjunction with interaction data. Notwithstanding their widespread appeal, previous assessments have revealed significant deficiencies in these complimentary platforms, such as inadequate coverage, variable severity classification, absence of comprehensive management guidance, and inconsistent updating practices (11-13).

Considering the prevalent application of complimentary DDI checkers in environments with limited resources, it is essential to scrutinize their precision, comprehensiveness, and reliability in relation to conventional subscription-based resources. This research endeavours to address that deficiency by methodically assessing Medscape, Drugs.com, and DrugBank in comparison to Lexidrug™ as a benchmark standard**.**

MATERIALS AND METHODS

This cross-sectional comparative study was conducted to evaluate the performance of free online drug-drug interaction (DDI) checkers relative to a standard subscription-based reference in the Department of Pharmacology, Madras Medical College, Chennai, India. Data collection was undertaken over a one-month period of June 2025, following approval from the Institutional Ethics Committee (IEC). Lexidrug™ (Lexicomp), a subscription-based database widely regarded as a gold standard due to its evidence-based content, peer-reviewed updates, and comprehensive coverage of clinically relevant interactions, was used as the reference standard for this study. Drug pairs were selected using Stockley's Drug Interactions (11th edition). A total of 150 pairs were included, consisting of 140 interacting and 10 non-interacting pairs.

Inclusion criteria: Drug pairs involving at least one cardiovascular agent, classified according to the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system, pairs with a clearly defined interaction status (interacting or non-interacting) in Lexidrug™; availability of both drugs in all four platforms under evaluation.

Exclusion Criteria: Duplicate drug pairs with identical mechanisms of interaction, Drug pairs unavailable in any of the free online databases tested.

Three freely available online drug interaction checkers were evaluated: 1. Medscape Drug Interaction Checker (Medscape, WebMD LLC), 2.Drugs.com Interaction Checker (Drugs.com, Drugsite Trust). 3.DrugBank Interaction Database (Wishart Research Group, University of Alberta). These platforms were compared against Lexidrug™ as the reference.

Each of the 150 drug pairs was entered individually into Medscape, Drugs.com, and DrugBank. For each pair, the following data such as presence of interaction, severity grading, mechanism of interaction, clinical management recommendations and references were collected. The same drug pairs were also verified in Lexidrug™, which served as the gold standard. To evaluate the comprehensiveness of the information provided, a 4-point completeness score was applied to each checker including mechanism of interaction (1 point), severity grading (1 point), clinical management advice (1 point) and references (1 point). The maximum possible score for each drug pair was 4 points, with higher averages indicating greater completeness.

The collected data was analyzed using SPSS v.26.0. The diagnostic accuracy measures including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using Lexidrug™ as the reference. Agreement in severity grading between each free checker and Lexidrug™ was measured using Cohen's kappa coefficient (κ).

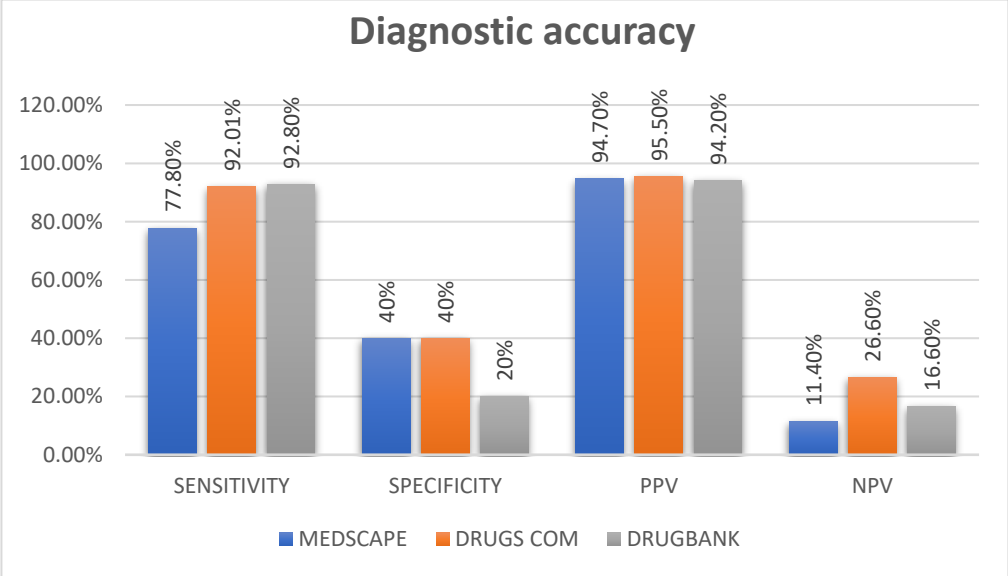
RESULTS

Table 1. Matrix for DDI detection by free online checkers compared with Lexidrug™

Checker	True Positives	False Positives	False Negatives	True Negatives
Medscape	109	6	31	4
Drugs.com	128	6	11	4
Drug Bank	130	8	10	2

Medscape identified 109 true positives and 4 true negatives, but missed 31 interacting pairs (false negatives). Drugs.com performed better, detecting 128 true positives with only 11 false negatives. DrugBank demonstrated comparable performance with 130 true positives and 10 false negatives, though its specificity was notably lower due to a higher rate of false positives (n = 8) (Table 1).

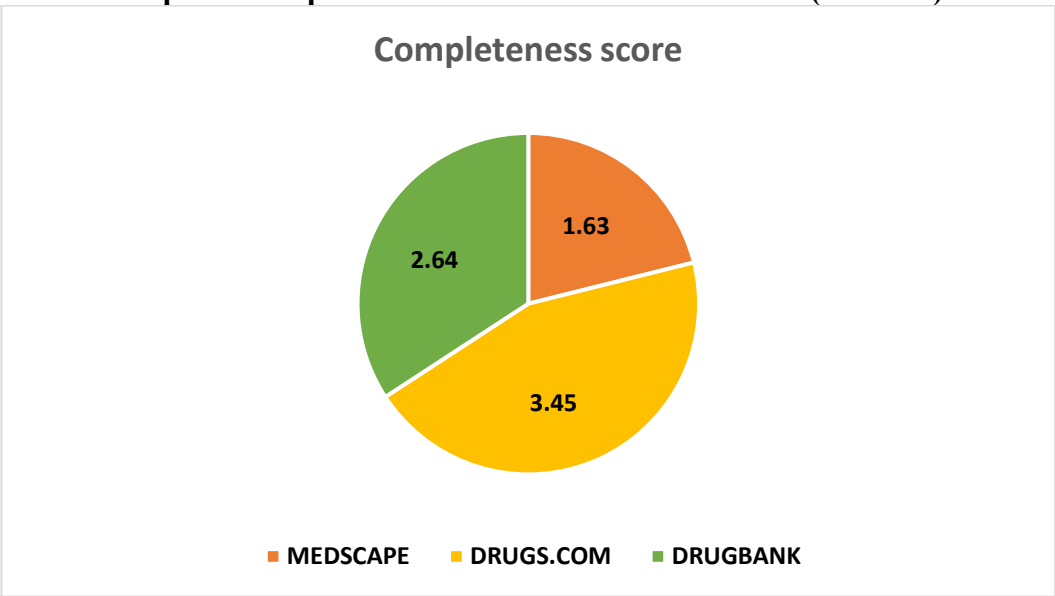
Graph 1. Diagnostic accuracy of free DDI checkers compared with Lexidrug™



In terms of sensitivity, DrugBank achieved the highest sensitivity (92.9%), followed closely by Drugs.com (92.1%). Medscape demonstrated lower sensitivity (77.9%), indicating a greater likelihood of missing clinically relevant interactions. In terms of specificity, Medscape and Drugs.com performed equally with moderate specificity (40.0%), while DrugBank had a lower specificity (20.0%), reflecting a higher number of false positives.

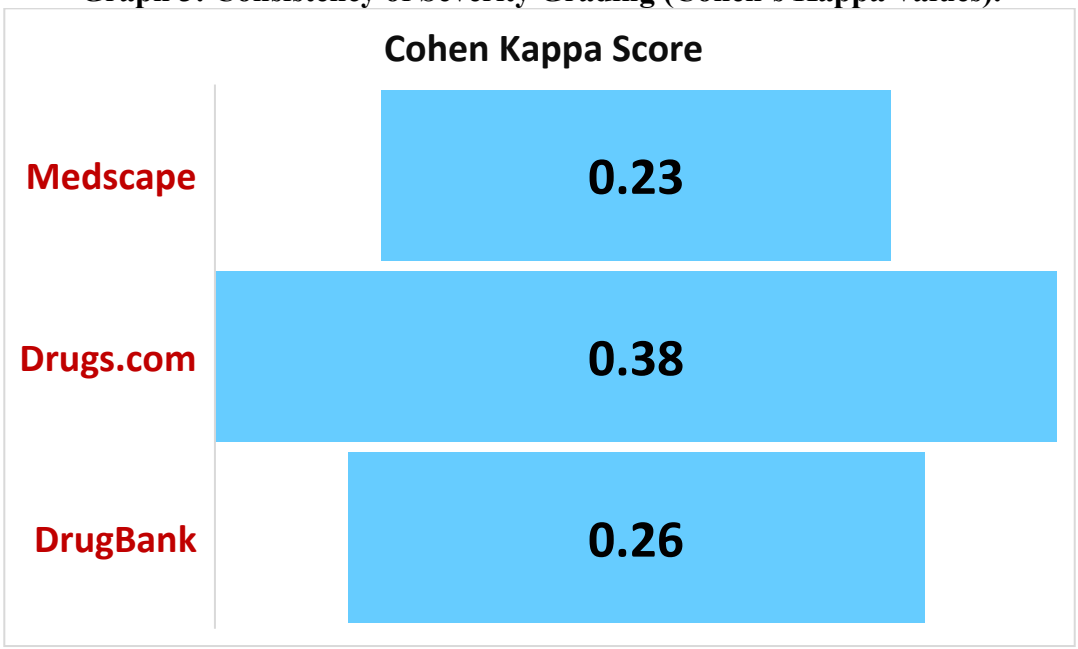
The positive predictive value of all three platforms showed strong PPVs (>94%), suggesting that when an interaction was flagged, it was highly likely to be a true interaction. The negative predictive values were notably low across all platforms, with Drugs.com performing relatively better (26.7%), followed by DrugBank (16.7%) and Medscape (11.4%). This indicates limited reliability in ruling out interactions (Graph 1).

Graph 2: Completeness Scores of DDI Information (Out of 4).



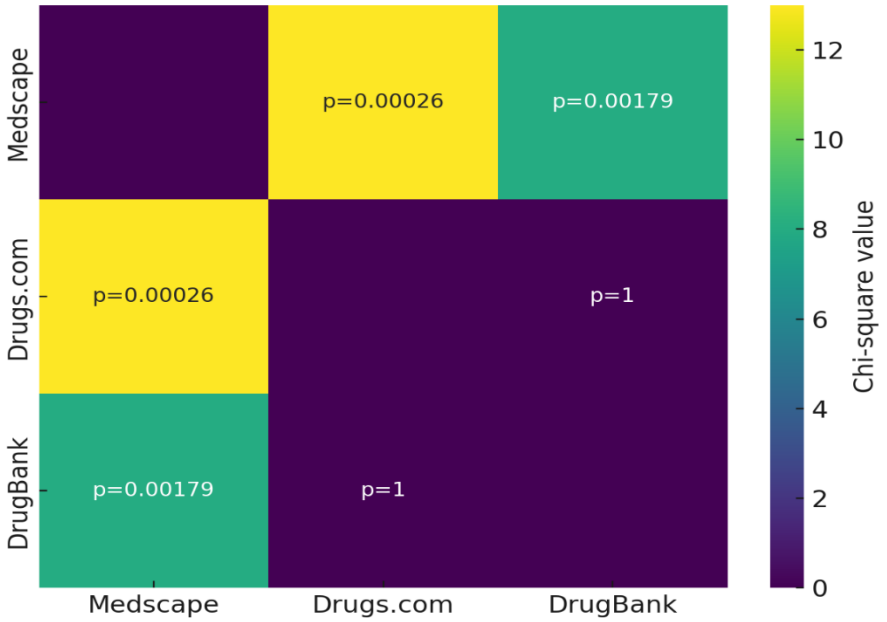
Among the platforms, Drugs.com achieved the highest score (3.45/4), reflecting the most comprehensive and clinically relevant information. DrugBank scored 2.64, demonstrating good pharmacological detail but limited clinical guidance, particularly in management advice. Medscape recorded the lowest score (1.63), indicating less consistent provision of interaction details and supporting references. (Graph 2).

Graph 3: Consistency of Severity Grading (Cohen's Kappa Values).



Cohen's kappa coefficient was used to assess agreement between the severity grading of free checkers and Lexidrug™. The Agreement was only **fair** for all platforms, with Drug.com showing the highest ($\kappa = 0.38$), followed by DrugBank ($\kappa = 0.26$) and Medscape ($\kappa = 0.23$) (Graph 3).

Graph 4: Pairwise Chi-square Comparison of DDI Checkers.



Both Medscape & Drugs.com and Medscape & DrugBank comparisons showed statistically significant differences, suggesting variability in their DDI detection outputs. In contrast, Drugs.com and DrugBank showed no significant difference, implying closer alignment in their interaction detection patterns (Graph 4).

DISCUSSION

This study evaluated the diagnostic efficacy, thoroughness, and reliability of three prominent free online drug-drug interaction (DDI) checkers Medscape, Drugs.com, and DrugBank by comparing them to Lexidrug™, a subscription-based benchmark of excellence. The findings revealed that Drugs.com and DrugBank exhibited elevated sensitivity levels exceeding 90%, underscoring their robust proficiency in identifying potential interactions. This is consistent with earlier assessments indicating that openly available platforms can effectively identify potential drug-drug interactions, thus reducing the likelihood of overlooked interactions and the related dangers of adverse drug reactions. Nonetheless, the diminished sensitivity of Medscape, approximately 78%, indicates an increased probability of false negatives, which could present considerable clinical risk, especially concerning high-alert medications like anticoagulants and antiarrhythmics (4).

The lack of specificity results in false positives, potentially leading to alert fatigue, a situation in which clinicians may disregard or override warnings due to an overwhelming number of alerts that hold minimal clinical relevance. Prior research has underscored alert fatigue as a significant constraint of drug interaction software, especially when specificity is diminished (7,11). While the sensitivity levels were deemed acceptable, the specificity across all platforms remained unsatisfactory (≤40%), aligning with previous comparative evaluations that indicated a propensity for free interaction checkers to exaggerate risks (12, 13).

Among the three complimentary platforms evaluated, Drugs.com exhibited the most comprehensive completeness scores, consistently offering detailed explanations of mechanisms, severity assessments, and references, alongside adequately thorough clinical management guidance. In contrast, DrugBank, while possessing considerable pharmacological depth, was observed to be less focused on clinical applications, often missing actionable management recommendations. This observation underscores its fundamental purpose as a biochemical and pharmacoinformatics resource, rather than serving as a specialized clinical decision support tool (11). Medscape provided a moderate level of completeness; however, its content exhibited a lack of consistent updates, reflecting the observations made by Vonbach et al. and Vitry, who highlighted the variability in updating and inconsistency prevalent among free platforms (12, 13).

A significant observation was the low-to-moderate concordance (κ = 0.23–0.38) between the free tools and Lexidrug™ in terms of severity classification. This inconsistency engenders a degree of uncertainty for prescribers, as analogous drug pairs may receive disparate evaluations contingent upon the platform employed. This resonates with the findings of Abarca et al., who identified notable inconsistencies in severity ratings among recognized compendia (5). The variability in severity grading poses a significant risk, potentially leading to undertreatment when severity is underestimated, or conversely, to overtreatment and unwarranted adjustments in therapy when severity is overstated.

Roblek et al. highlighted that although DDI software enhances medication safety, notable limitations such as incomplete coverage and inconsistent severity assessment persist as considerable obstacles (11). In a similar vein, Vitry's comparative analysis indicated that subscription-based tools exhibit variations, albeit to a lesser extent than their free database counterparts (13). Aguilar DR et al. documented that a total of 797 dental patients were simultaneously utilizing psychotropic medication in conjunction with other pharmaceuticals. The number of patients with DDI varied among different sources: Micromedex® documented 366, Medscape® recorded 473, and DrugBank reported 736. The level of agreement among the DDI checkers was found to be low, as evidenced by a Fleiss' kappa value of 0.165 ($p<0.001$). The online DDI checkers assessed in this study revealed inconsistencies in their ability to detect interactions and showed a low level of agreement among themselves (14). Shariff A et al. undertook a comprehensive review of eight distinct drug interaction resources, which encompass Micromedex®, Portable Electronic Physician Information Database©, UpToDate®, Medscape.com drug interaction checker, Drugs.com drug interaction checker, Stockley's Drug Interactions (ninth edition, 2010), Drug Interactions Analysis & Management: Facts and Comparisons 2014 (ninth edition, 2014), and the drug interaction appendix of the British National Formulary-76. It was determined that both UpToDate® and the Portable Electronic Physician Information Database© attained an exceptional scope score of 100% each. The completeness score for Drug Interaction Analysis & Management: Facts and Comparisons 2014 was a perfect 100% (15). Yaowaluk T et al. discerned a total of 154 potential drug-drug interaction pairs from the databases, comprising 100 from Micromedex and 118 from WebMD. Nineteen drug-drug interactions were classified as severe by both databases. The concordance among the databases was minimal (kappa = −0.126, $p = 0.008$), indicating significant inconsistencies in the categorization of DDI severity (16).

This study's primary strength is its methodical assessment of 150 drug pairs sourced from Stockley's Drug Interactions, which guarantees both clinical significance and methodological precision. The emphasis on cardiovascular drug pairs underscores their significance, particularly in light of the elevated risk for clinically meaningful drug-drug interactions. Nonetheless, the research faced constraints due to the inclusion of merely three complimentary platforms and dependence on Lexidrug™ as the exclusive reference standard. Expanding the scope of comparisons to include supplementary subscription-based databases could provide deeper insights. Furthermore, this study did not evaluate usability, speed, or user interface, factors that also play a significant role in clinical adoption.

CONCLUSION

In conclusion, while free online DDI checkers such as Drugs.com, DrugBank, and Medscape provide valuable support in detecting potential interactions, significant limitations exist in terms of specificity, completeness, and consistency. Drugs.com emerged as the most reliable among the free tools, but none matched the comprehensiveness and consistency of Lexidrug™. For optimal clinical decision-making, especially in high-risk patient populations, subscription-based resources remain indispensable.

REFERENCES

1. Becker ML, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. *Pharmacoepidemiol Drug Saf*. 2007;16(6):641-651.

2. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57-65.
3. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. Eur Geriatr Med. 2021 Jun;12(3):443-452.
4. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*. 2003;289(13):1652-1658.
5. Abarca J, Malone DC, Armstrong EP, et al. Concordance of severity ratings provided in four drug interaction compendia. *J Am Pharm Assoc (2003)*. 2004;44(2):136-141.
6. Stockley IH, ed. *Stockley's Drug Interactions*. 11th ed. London: Pharmaceutical Press; 2022.
7. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5 Pt 2):397-403.
8. Medscape. Drug Interaction Checker. Available at: https://reference.medscape.com /drug-interactionchecker. Accessed August 2025.
9. Drugs.com. Drug Interactions Checker. Available at: https://www.drugs.com/ drug_ interactions.html. Accessed August 2025.
10. Wishart DS, Knox C, Guo AC, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res*. 2006;34(Database issue):D668-D672.
11. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: a systematic review. *Eur J Clin Pharmacol*. 2015;71(2):131-142.
12. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Evaluation of frequently used drug interaction screening programs. *Pharm World Sci*. 2008;30(4):367-374.
13. Vitry AI. Comparative assessment of four drug interaction compendia. Br J Clin Pharmacol. 2007 Jun;63(6):709-14. doi: 10.1111/j.1365-2125.
14. Aguilar DR, Cruz AJS, Martins MAP, Abreu MHNG. A comparative analysis of three online drug-druginteraction checkers: A short communication. Pesqui Bras Odontopediatria Clín Integr. 2024; 24:e230193.
15. Shariff A, Belagodu Sridhar S, Abdullah Basha NF, Bin Taleth Alshemeil SSH, Ahmed Aljallaf Alzaabi NA 4th. Assessing Consistency of Drug-Drug Interaction-Related Information Across Various Drug Information Resources. Cureus. 2021 Mar 8;13(3):e13766.
16. Yaowaluk T, Tangpanithandee S, Techapichetvanich P, Khemawoot P. Discordance in Drug–Drug Interaction Alerts for Antidotes: Comparative Analysis of Electronic Databases and Interpretive Insights from AI Tools. *Drug Des Devel Ther*. 2025;19:7427-7443