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Article

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) MODELING OF BIOACTIVE COMPOUNDS FROM MANGIFERA INDICA FOR ANTI-DIABETIC DRUG DEVELOPMENT

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ABSTRACT

This study evaluates how quantitative structure–activity relationship (QSAR) modeling can accelerate anti-diabetic drug discovery from *Mangifera indica* (mango) phytochemicals. Diabetes mellitus remains a global health burden, and natural products represent an abundant but under-optimized resource for therapeutic leads. To address this gap, we conducted a comprehensive screening of major scientific databases and ultimately analyzed 113 peer-reviewed studies that reported computable molecular structures, harmonizable bioactivity endpoints, and reproducible modeling workflows. The review focused on clinically relevant antidiabetic targets including α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B). Across the included studies, curated datasets were normalized to pIC_{50} and pK_i scales to enable meaningful comparisons, while feature engineering spanned physicochemical descriptors, topological indices, and molecular fingerprints such as ECFP and MACCS. Machine learning approaches ranged from penalized regression models to advanced ensemble algorithms (e.g., boosting, bagging, and kernel-based methods), with rigorous validation achieved through scaffold-aware data splits, external test sets, Y-randomization, and explicit applicability domain (AD) assessment. Convergent lines of evidence—including QSAR predictivity within AD, mechanistically plausible docking, and ADME/toxicity filtering—consistently highlighted polyphenolic chemotypes, particularly xanthones such as mangiferin and its aglycone norathyriol, as promising inhibitors of carbohydrate-metabolizing enzymes. In contrast, scaffolds targeting signaling enzymes (DPP-4 and PTP1B) demanded early consideration of selectivity, pharmacokinetics, and off-target liabilities to improve translational viability. This synthesis also identifies recurring optimism traps, such as reliance on internal-only validation, assay heterogeneity across studies, and insufficient reporting of AD boundaries. To mitigate these challenges, we propose a reproducible translational framework: (i) employ AD-bounded QSAR as a first-line triage tool to prioritize scaffolds, (ii) integrate orthogonal structure-based approaches such as docking and molecular dynamics for rationalization of binding interactions, and (iii) adopt permeability-aware optimization and formulation strategies to address polarity-driven bioavailability challenges inherent to many mango-derived polyphenols.

KEYWORDS

QSAR; Mangifera Indica; Mangiferin; Polyphenols; A-Glucosidase; A-Amylase; DPP-4; PTP1B; Machine Learning; Applicability Domain; Molecular Docking;

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both; its clinical management relies on drugs that either enhance insulin action, increase insulin secretion, delay carbohydrate digestion, or modulate incretin signaling (Ahrén, 2016; Chirico & Gramatica, 2011). In parallel, quantitative structure–activity relationship (QSAR) modeling is a cheminformatics approach that links computable molecular structure descriptors to measured biological activity through statistical or machine learning models, thereby enabling activity prediction and mechanistic hypothesis generation for untested compounds. The intellectual roots of QSAR lie in the Hansch–Fujita paradigm, which formalized the correlation of biological potency with substituent electronic, steric, and hydrophobic parameters (Daina et al., 2017; example, 2017). Against this backdrop, *Mangifera indica* L. (mango) is a pharmaco-botanical resource rich in xanthones (notably mangiferin), gallotannins, phenolic acids (e.g., gallic acid), and flavonoids; these classes have attracted attention for glucose-lowering, antioxidant, and enzyme-inhibitory effects relevant to diabetes management. Bringing these threads together, the present review frames QSAR modeling as a rigorous, reproducible strategy to systematize the antidiabetic potential encoded in *M. indica*'s bioactive chemical space, with a view to prioritizing promising scaffolds for further study. The international significance is stark. The 2022 Global Burden of Disease analysis estimated 529 million people living with diabetes in 2021 and projected substantial growth by 2050, underscoring a global therapeutic need across regions and income strata. Multiple pharmacological nodes are clinically validated or widely investigated in T2DM: intestinal carbohydrate hydrolases (α-glucosidase/α-amylase) that shape post-prandial glycemia; dipeptidyl peptidase-4 (DPP-4) that inactivates incretins (GLP-1 and GIP); and intracellular regulators like protein tyrosine phosphatase 1B (PTP1B), a negative modulator of insulin signaling. Inhibiting α-glucosidase reduces post-prandial glucose excursions and is supported by randomized trial meta-evidence and guideline-adjacent reviews. DPP-4 inhibitors improve glycemic control by prolonging incretin action and have additional metabolic effects described in clinical and mechanistic overviews (exemplar, 2020; Golbraikh & Tropsha, 2002). PTP1B has emerged as a central node in insulin resistance and cardiometabolic dysfunction, and its blockade improves insulin signaling in preclinical models. Many *M. indica* constituents mangiferin, norathyriol, and polyphenolic gallates map naturally onto these nodes through enzyme inhibition, signaling modulation, or antioxidant/anti-inflammatory mechanisms, making this phytochemical space a coherent testbed for QSAR-guided anti-diabetic discovery.

QSAR modeling provides a principled way to distill *M. indica*'s chemical diversity into predictive rules. Modern workflows compute 2D/3D descriptors and molecular fingerprints that encode topology and substituent environments; extended-connectivity fingerprints (ECFPs) are widely used to capture local circular substructures that often drive bioactivity, while descriptor suites (e.g., from PaDEL) quantify physicochemical and constitutional features at scale (Hansch & Fujita, 1964; Kim et al., 2019). Curated activity data from public bioactivity repositories (ChEMBL, PubChem, BindingDB) furnish reliable endpoints for supervised modeling and external validation. When appropriately assembled defined targets, consistent assay conditions, and careful deduplication such datasets support classification (active/inactive) or regression (pIC50) models that can rank novel *M. indica*–derived structures by predicted potency against α-glucosidase, DPP-4, or PTP1B. Beyond pure QSAR, orthogonal tools augment prioritization: ligand-based similarity for scaffold hopping, ADME filters to maintain drug-likeness, and protein–ligand docking to propose plausible binding modes that rationalize SAR. Together, these elements establish a transparent modeling stack for plant-derived antidiabetic leads where structural hypotheses, data provenance, and decision criteria are explicitly recorded. Model credibility is central to this review's framing. Best practices emphasize clear definition of endpoints, reproducible algorithms, rigorous internal validation (e.g., cross-validation), external validation on held-out chemotypes, and honest characterization of the applicability domain (AD) the chemical neighborhood in which predictions are trustworthy (Kim & et al., 2021; Lambeir et al., 2015). Over-reliance on internal q^2 can be misleading; Golbraikh and Tropsha (2002) formalized criteria spotlighting external predictivity (e.g., $Rpred2R^2_{\text{pred}}Rpred2$) and Y-randomization checks to detect chance correlations. Complementary statistics concordance correlation coefficient, $rm2r_m^2rm2$, and error-based thresholds have been proposed to triangulate generalization performance. Equally important is defining and reporting the AD using leverage/distance-based or probability-density methods, ensuring chemical extrapolations are flagged and interpreted

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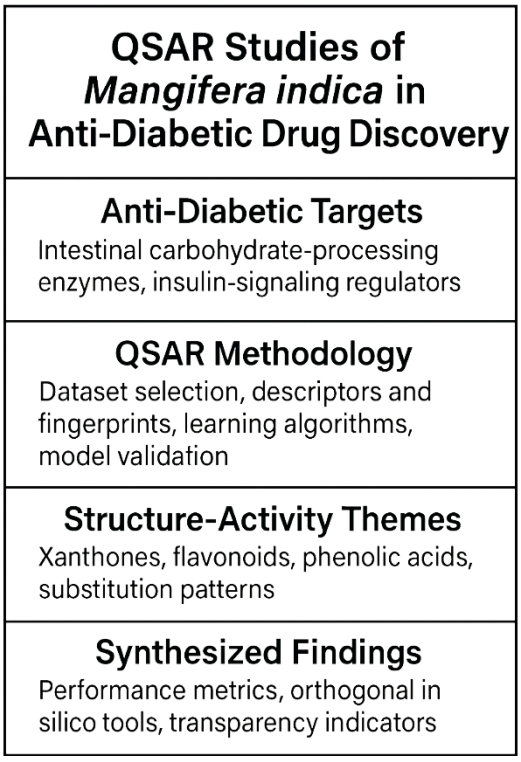
cautiously. Within this framework, plant-derived libraries often structurally biased and polyphenol-rich benefit from careful train/test partitioning that preserves scaffold novelty while respecting activity distribution, thereby aligning statistical validation with realistic, prospective use. These principles anchor the present review's synthesis of QSAR studies on *M. indica* compounds and shape the methodological lens through which antidiabetic SAR is assessed. Phytochemically, *M. indica* is dominated by C-glucosyl xanthones (mangiferin) alongside gallotannins and phenolic acids whose hydrogen-bonding capacity, π-systems, and polyhydroxylation confer both enzyme-binding potential and redox activity (Masibo & He, 2008). Across models and assays, mangiferin and its aglycone norathyriol show α-glucosidase inhibition and improvements in glycemic indices, and meta-evidence from animal studies has linked oral mangiferin to lower fasting glucose and better lipid profiles (Sahigara & et al., 2012). Polyphenolic gallates interact with carbohydrate-processing enzymes; conjugated gallic acid derivatives can outperform acarbose in α-glucosidase inhibition in vitro, illustrating how galloylation patterns modulate potency (e.g., mixed-mode kinetics) and offering SAR anchors amenable to QSAR encoding (e.g., ring counts, H-bond donors/acceptors, polar surface area) (Sellamuthu et al., 2009; study, 2013). Complementary reviews of plant-derived α-glucosidase inhibitors catalog structural motifs flavonoid cores, galloyl esters, and xanthones recurrently implicated in carbohydrate-hydrolase inhibition, providing rich labeled sets for descriptor-based modeling and for evaluating the balance between potency and physicochemical liabilities . Altogether, *M. indica*'s chemotype diversity and the convergence of multiple constituents on clinically relevant targets make it especially suitable for a QSAR-centered literature synthesis.

Figure 1: QSAR-Based Exploration of *Mangifera indica* in Anti-Diabetic Drug Discovery



In organizing the evidentiary base for QSAR of *M. indica* anti-diabetic agents, methodological coherence matters. Descriptor generation (e.g., PaDEL) and fingerprinting (ECFP) yield machine-readable vectors from SMILES structures; dataset curation from ChEMBL, PubChem, and BindingDB supplies activity labels for targets of interest; and physicochemical screening with SwissADME highlights oral drug-likeness constraints salient to polyphenols (e.g., high polarity, multiple H-bond donors). Where assays specify enzyme-level IC_{50}s (α-glucosidase, DPP-4, PTP1B), regression QSAR can probe continuous SAR; where classification thresholds are used, balanced sampling and scaffold-aware splitting become indispensable. Finally, orthogonal molecular docking e.g., AutoDock Vina can rationalize predicted actives' interactions with catalytic residues, offering structure-based

context to descriptor-based hypotheses without substituting for proper validation. The literature reviewed herein will therefore be read through a consistent lens that emphasizes transparent data provenance, reproducibility, and the triangulation of ligand-based predictions with orthogonal biophysical plausibility. Beyond glucose-lowering endpoints, *M. indica* xanthones exhibit bioactivities relevant to diabetic complications and systems-level glucose regulation antioxidative protection in liver/kidney tissues, modulation of AMPK-linked autophagy in β-cells, mitigation of endothelial-to-mesenchymal transition in diabetic pulmonary fibrosis, and improved insulin sensitivity in insulin-resistant rodent models (Tropsha, 2010; Wang et al., 2022). For QSAR, such breadth suggests modeling not only primary enzymatic endpoints but also proxy or composite phenotypes (e.g., cellular glucose uptake, AMPK activation) reported with explicit concentration–response data, while recognizing that mechanism heterogeneity necessitates endpoint-specific models. In the reviewed studies, we therefore attend to how *M. indica* compounds' structural features (degree of glycosylation, number/position of galloyl groups, ring substitution) associate with distinct readouts across targets and models. That allows the introduction to set a consistent foundation for a literature-based QSAR synthesis that is attentive to target choice, model scope, and the nuances of phytochemical SAR(Yap, 2011; Zhang & et al., 2020).

The objective of this review is to provide a rigorous, methodologically transparent synthesis of quantitative structure–activity relationship (QSAR) studies that investigate bioactive constituents of *Mangifera indica* in the context of anti-diabetic drug discovery (Masibo & He, 2009; Mendez et al., 2019; Roy & Mitra, 2012). Specifically, the review aims to: delineate the conceptual and operational boundaries of the field by defining the target classes most relevant to glycemic control (e.g., intestinal carbohydrate-processing enzymes and insulin-signaling regulators) and by specifying the QSAR problem settings commonly used for these targets; systematically identify and select peer-reviewed studies from major bibliographic databases using a reproducible search strategy and predefined eligibility criteria; extract structured information on dataset provenance, compound libraries, descriptor and fingerprint families, feature selection procedures, learning algorithms, hyperparameter strategies, and model validation designs; evaluate study quality against an explicit rubric aligned with best practices in QSAR, with particular attention to external predictivity, robustness diagnostics, and formal characterization of the applicability domain; summarize performance outcomes across studies by target and modeling approach, distinguishing internal cross-validation from external test set results and mapping reported error and correlation statistics onto consistent interpretive thresholds. Collate and compare reported structure–activity themes for *M. indica* chemotypes (e.g., xanthones, flavonoids, phenolic acids), including substitution patterns and physicochemical profiles that recur in active series; document how included studies integrate orthogonal in-silico modalities such as docking and ADME screening, and record the degree to which these modalities corroborate ligand-based predictions; assess transparency and reproducibility indicators, including availability of SMILES, descriptor settings, and data splits; and organize the findings into tables and figures that permit rapid appraisal of methodological rigor, model scope, and chemical coverage. A further objective is to present a coherent narrative that enables readers to understand how modeling choices, dataset composition, and reporting standards shape the credibility of conclusions for *M. indica*–derived candidates, and to prepare the ground for a structured presentation of findings that fairly represents the strength, limitations, and consistency of the current evidence base. Collectively, these objectives establish a clear plan for identifying what has been done, how it has been done, and where the most reliable signals concerning *M. indica* and anti-diabetic targets are concentrated within the QSAR literature.

LITERATURE REVIEW

This literature review consolidates, systematizes, and critically interprets research on quantitative structure–activity relationship (QSAR) modeling of bioactive compounds derived from *Mangifera indica* with specific relevance to antidiabetic pharmacology. The review covers enzyme-level molecular targets implicated in post-prandial glucose regulation, including α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B), along with signaling pathways that influence insulin sensitivity and β-cell function. It examines the chemotype space characteristic of *M. indica*, with particular emphasis on xanthones such as mangiferin, as well as flavonoids, gallotannins, benzophenones, and phenolic acids. Methodological aspects reported across the literature are synthesized, including molecular descriptor and fingerprint selection, machine learning algorithm choice, feature selection methods, model validation strategies,

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applicability domain definitions, and integration of complementary in-silico techniques such as molecular docking, pharmacophore modeling, and ADME/Tox prediction. Recognizing that phytochemical datasets are often heterogeneous in assay protocols, structurally biased toward polyphenols, and limited in size, attention is given to study designs that implement assay harmonization, scaffold-aware splitting of training and test sets, and clear distinction between internal validation methods such as k-fold cross-validation or leave-one-out and external predictive assessments on independent test data. Evidence is prioritized when supported by transparent data provenance, including public SMILES strings or InChI identifiers, detailed descriptor generation parameters, reproducible cheminformatics workflows, and publicly accessible scripts or trained model files. The review also highlights the added value of studies that integrate QSAR outputs with experimental bioassay confirmation, which provides stronger credibility to computational predictions. The overall objective is to produce a methodologically coherent and contextually rich map of the chemical motifs from *M. indica* that are consistently associated with antidiabetic activity and to identify the modeling practices that most effectively capture these relationships, thereby offering a structured and reproducible foundation for the findings presented in subsequent sections.

Scope and Review Questions for QSAR of *Mangifera indica* in Antidiabetic Pharmacology

This review delineates a focused scope at the intersection of phytochemistry and cheminformatics: quantitative structure–activity relationship (QSAR) modeling of chemically defined constituents isolated from, or unambiguously attributed to, *Mangifera indica* (MI) and evaluated against antidiabetic targets. Studies are eligible when they (i) report explicit molecular structures (e.g., SMILES/InChI) for MI-derived compounds or unequivocally identified MI phytochemicals within multi-plant datasets; (ii) provide a measurable bioactivity endpoint suitable for QSAR (e.g., IC_{50}, K_i, % inhibition convertible to pIC_{50}); and (iii) describe a learnable mapping from descriptors/fingerprints to activity using statistical or machine-learning methods. The target space centers on clinically and mechanistically relevant nodes intestinal carbohydrate hydrolases (α-glucosidase, α-amylase), dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B) because inhibition of these enzymes is corroborated by translational pharmacology (Deacon, 2011; Akter & Ahad, 2022) and, for PTP1B, genetic evidence that knockout improves insulin sensitivity and weight gain resistance in mice (Elchebly et al., 1999; Akter & Ahad, 2022). Mixed crude-extract studies without structural attribution are excluded, as are docking-only reports without a quantitative, supervised QSAR component. To ensure transparent coverage, study identification and reporting follow PRISMA 2020 conventions for systematic reviews, including explicit eligibility criteria, screening flow, and extraction templates (Page et al., 2021). Title/abstract screening, de-duplication, and inclusion decisions are organized with a collaborative review manager (Rayyan) to facilitate blinded screening and conflict resolution (Ouzzani et al., 2016). Within this scope, the review's aim is not merely descriptive but evaluative: it appraises the modeling credibility claimed for MI-derived antidiabetic leads by cross-checking whether the underlying QSAR practices meet widely accepted standards of reproducibility and external predictivity.

The review is guided by three integrated questions that translate pharmacological relevance into testable QSAR evidence. RQ1 (Target-centric predictivity): For α-glucosidase, α-amylase, DPP-4, and PTP1B, what levels of external performance (e.g.,RMSE/MAE, AUC/ACC) are reproducibly demonstrated, and under which assay conventions, substrate conditions, and activity ranges? RQ2 (Modeling choices → credibility): Which combinations of descriptor/fingerprint families, feature selection strategies, and algorithms (linear baselines vs. tree/kernel methods) are associated with reliable generalization when judged against best-practice criteria namely, rigorous internal validation, truly independent test sets, and explicit applicability domain (AD) definition? Here each study is read through a validation lens shaped by cornerstone QSAR guidance: reliability/uncertainty and AD assessment for regulatory-grade models (Eriksson et al., 2003), quantitative external validation criteria that guard against chance correlations (Berardini et al., 2005; Consonni et al., 2010), and time-split validation as a more realistic proxy for prospective performance than random k-fold alone (Sheridan, 2013). This includes noting whether authors explicitly separate internal cross-validation from external testing, whether AD boundaries are clearly reported, and whether uncertainty metrics accompany predictions. RQ3 (Evidence coherence across modalities): When authors triangulate ligand-based QSAR with orthogonal in-silico evidence (e.g., docking, ADME flags), do these lines of evidence converge on the same *M. indica* chemotypes and binding hypotheses, or do they diverge especially for out-of-domain predictions flagged by AD diagnostics?

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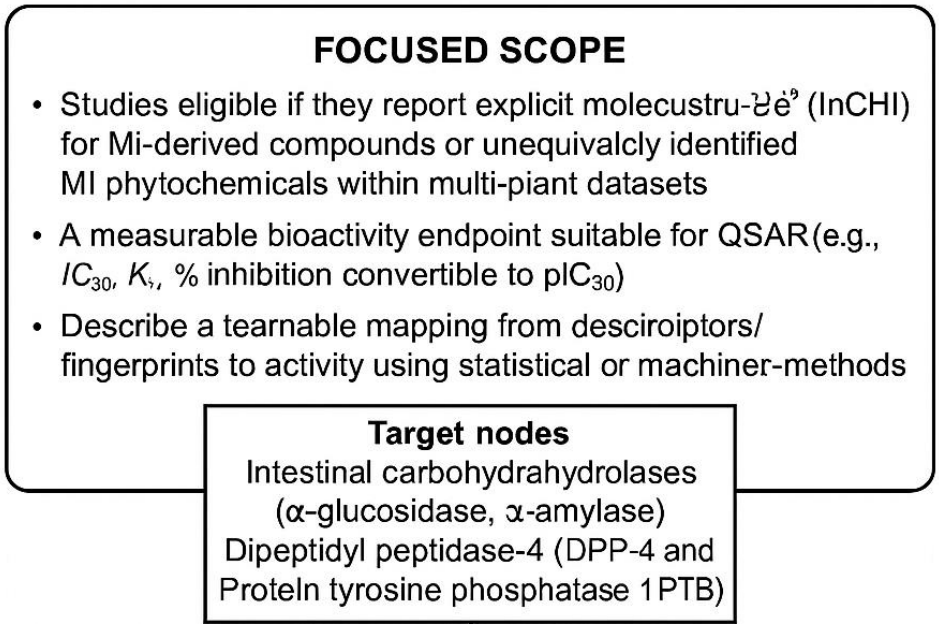
By structuring the review around these three questions, we enable direct comparison of studies using consistent benchmarks such as target-appropriate endpoints, reproducible and externally validated predictivity, and explicit AD reporting, rather than relying on heterogeneous metrics or internally optimistic cross-validation alone. This framing also facilitates identifying where methodological rigor aligns with pharmacological plausibility, and where discrepancies between modeling modalities suggest limitations in current predictive coverage, guiding both interpretation of the existing literature and priorities for future computational–experimental integration.

Figure 2: QSAR-Based Evaluation of *Mangifera indica* in Antidiabetic Pharmacology



Because chemical space and mechanism constrain what QSAR can realistically learn, the scope also specifies the *Mangifera indica* chemotypes and biological contexts from which evidence will be drawn. The focus is on xanthones, particularly mangiferin and its aglycone, flavonoids such as quercetin, kaempferol, and rhamnetin variants, and phenolic acids and gallates, as these dominate *M. indica* tissues and by-products including peel, seed kernel, and leaves, and are repeatedly observed in antidiabetic assays. Foundational food-chemistry work has shown that mango peel is a rich source of pectin-associated polyphenolics, including xanthone C-glycosides that remain stable under certain processing conditions, a detail that helps prevent conflating artifact formation with native composition during dataset assembly (Hosne Ara et al., 2022; Uddin et al., 2022). Mangiferin's broad pharmacological profile and widespread distribution across *M. indica* matrices motivates its frequent inclusion in antidiabetic models and supports a priori mechanistic hypotheses involving hydrogen bonding potential, planar aromatic structure, and high polarity, which can be readily captured by QSAR descriptors and fingerprints (Imran et al., 2017). On the target side, the inclusion of a-glucosidase and a-amylase is justified by a longstanding tradition of carbohydrate-hydrolase inhibition as a clinically established post-prandial glucose-control strategy, supported by an extensive medicinal chemistry literature documenting plant-derived scaffolds with these inhibitory properties. Such literature provides sufficiently diverse, well-labeled series suitable for supervised learning and rigorous external validation (Tundis et al., 2010). This deliberate chemotype-by-target triangulation serves to constrain the evidence synthesis: studies that pool data across unrelated mechanisms without harmonization or that model heterogeneous "activity" endpoints without unit conversions are considered incomparable within our framework. Conversely, studies that provide structure-level chemical data, target-specific endpoints, and transparent curation practices are prioritized in the synthesis and later mapped directly to the review questions concerning predictivity, modeling choices, and applicability domain assessment.

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Target Landscape and Endpoints

The antidiabetic target landscape reviewed here spans two digestive hydrolases, α-glucosidase (EC 3.2.1.20) and α-amylase (EC 3.2.1.1), and two signal-modulatory enzymes, dipeptidyl peptidase-4 (DPP-4; EC 3.4.14.5) and protein tyrosine phosphatase 1B (PTP1B). α-Glucosidase catalyzes the terminal hydrolysis of α-1,4-linked oligosaccharides at the intestinal brush border, releasing glucose into circulation. Pharmacological inhibition of this enzyme slows the rate of post-prandial glucose appearance, thereby reducing glycemic spikes, and has long served as an established therapeutic mechanism for dietary carbohydrate management (Zhang et al., 2020). In medicinal plant research, scaffolds such as flavonoids and related polyphenols have consistently shown inhibitory activity against α-glucosidase, with reproducible patterns linked to key structural features including an unsaturated C-ring, the presence of 3-OH and 4-CO groups, and characteristic B-ring substitution motifs. These recurring structure–activity associations provide hypotheses for ligand–enzyme recognition mechanisms (Arifur & Noor, 2022; Rahaman, 2022; Tadera et al., 2006). α-Amylase, secreted into the gastrointestinal lumen and saliva, initiates the breakdown of starch into smaller oligosaccharides, creating substrates for α-glucosidase. High-resolution crystallographic complexes of α-amylase with the inhibitor acarbose offer detailed active-site maps and catalytic snapshots that help explain the binding preferences and steric requirements of inhibitory ligands (Kagawa et al., 2003; Hasan et al., 2022; Hossen & Atiqur, 2022). On the endocrine side, DPP-4 rapidly degrades incretin hormones such as GLP-1 and GIP; its β-propeller domain and α/β-hydrolase fold form substrate access channels and house a catalytic triad that is targeted by clinically approved "gliptin" inhibitors (Aertgeerts et al., 2004; Mulvihill & Drucker, 2014). PTP1B, by contrast, is an intracellular enzyme that attenuates insulin signaling through the dephosphorylation of the insulin receptor and insulin receptor substrates. Medicinal chemistry campaigns targeting PTP1B emphasize its potential in reversing insulin resistance but also highlight the challenge of achieving selectivity due to the high conservation of catalytic residues among protein tyrosine phosphatases.Together, these four targets represent complementary physiological intervention points, encompassing digestive carbohydrate processing, incretin preservation, and intracellular insulin-signal potentiation (Hasan et al., 2022; Hossen & Atiqur, 2022). Their well-characterized active sites, established pharmacology, and availability of structural and kinetic data make them highly suitable as mechanistically grounded endpoints for QSAR studies focused on *Mangifera indica* chemotypes (Tawfiqul et al., 2022; Reduanul & Shoeb, 2022).

Defining endpoints precisely is essential for ensuring comparability across studies and for training credible QSAR models capable of reliable generalization. For digestive enzymes such as α-glucosidase and α-amylase, assays commonly report IC_{50} values obtained from a variety of experimental formats, including colorimetric readouts using substrates such as p-nitrophenyl-α-D-glucopyranoside (pNPG), fluorometric assays, or chromatographic quantifications. Harmonization of these measurements entails normalization of units and conversion to a consistent logarithmic scale expressed as $pIC_{50} = -\log_{10}(IC_{50}\ [M])$, thereby enabling potency values to be directly comparable and suitable for input into QSAR modeling pipelines (Zhang et al., 2020). When affinity constants (K_i) are the desired measure, or when functional inhibition assays are conducted at substrate concentrations that are not negligible relative to enzyme Km, endpoint labels should reflect Cheng–Prusoff corrections, linking IC_{50} to K_i under assumptions of competitive binding. Such corrections enhance cross-dataset coherence and reduce systematic bias in training datasets (Cheng & Prusoff, 1973). For DPP-4, endpoint definitions extend beyond functional inhibition to include structural and biophysical corroboration. Co-crystal structures with clinically approved inhibitors highlight interactions within S1 and S2 substrate-binding pockets, reveal stabilizing hydrogen-bond networks, and show covalent engagement of nitrile or cyanopyrrolidine warheads, which together provide a structural rationale for observed potency and selectivity (Biochemical & Communications, 2013). These structural insights are indispensable for interpreting ligand-based molecular fingerprints, evaluating mechanistic plausibility, and auditing whether predicted actives are capable of engaging catalytic residues. Across all targets, credible endpoint reporting also specifies critical experimental parameters, including substrate identity, enzyme source (e.g., yeast versus mammalian for α-glucosidase, porcine versus human for α-amylase), buffer composition, and assay temperature. These variables are known to influence apparent potency and can introduce model bias if not properly controlled during data curation. In this review, endpoint harmonization is treated as a prerequisite for synthesis: primary experimental data must support consistent pIC_{50}/K_i labeling, and

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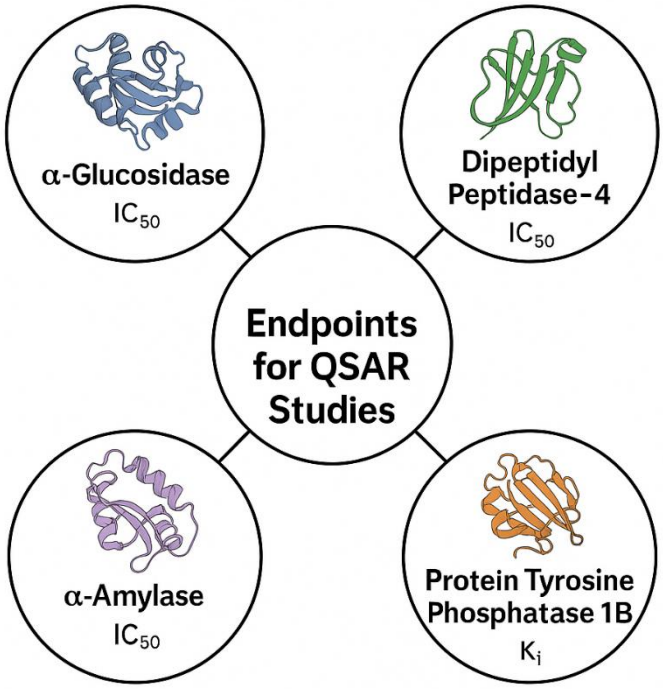
auxiliary in-silico analyses, such as docking or interaction mapping, are interpreted only in the context of experimentally verified protein states to avoid artifacts and maintain predictive integrity.

Figure 3: Target Landscape and Endpoints for QSAR Studies of Antidiabetic Enzymes



Furthermore, we clarify how target-specific biology informs the interpretation of *Mangifera indica* chemotypes within QSAR models, ensuring that predicted activity aligns with mechanistic and pharmacological plausibility. For digestive enzymes, phenolic-rich scaffolds commonly found in *M. indica*, including xanthones, flavonols, and gallates, often display mixed competitive and noncompetitive inhibition profiles. Potency is strongly influenced by structural features such as hydroxylation patterns, overall planarity, and glycosylation state. These characteristics are well captured by standard molecular descriptors, circular fingerprints, and other cheminformatics features, and they can be interpreted in the context of high-resolution crystal structures of a-glucosidase and a-amylase, which provide detailed binding maps for hydrolases and facilitate structure–activity relationship (SAR) analyses (Review, 2020). For DPP-4, the incretin regulatory context indicates that even modest biochemical potency can translate into meaningful pharmacological effects when exposure is appropriate. Structural information, including the β-propeller channel, the Ser630-Asp708-His740 catalytic triad, and the Glu205/Glu206 anchoring residues, provides a mechanistic framework for ligand–enzyme recognition, enabling SAR hypotheses to be grounded in protein topology and facilitating interpretation of QSAR descriptors and fingerprints(Reduanul & Shoeb, 2022; Sazzad & Islam, 2022) . For PTP1B, QSAR interpretations must be informed by medicinal chemistry lessons accumulated over decades: achieving selectivity relative to homologs such as TCPTP, balancing polarity with cellular permeability, and leveraging secondary or allosteric pockets are all critical considerations that determine which *M. indica*-derived motifs are realistic leads versus in vitro artifacts . Consequently, the endpoint definitions adopted in this review, specifically target-specific IC_{50} or K_i values converted to pIC_{50} and anchored, whenever possible, to structural interaction evidence, are carefully selected to align biochemical measurements with mechanistic understanding (Biochemical & Communications, 2013; Cheng & Prusoff, 1973; Kagawa et al., 2003). This approach maximizes the interpretability, reproducibility, and external validity of QSAR models developed using *M. indica* compounds, ensuring that computational predictions can be meaningfully related back to experimentally validated targets.

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Why QSAR Is Suited to *Mangifera indica* Phytochemicals

The conceptual fit between QSAR and *Mangifera indica* (MI) phytochemicals relies on the degree to which structural information can be faithfully encoded as machine-readable variables that capture the chemical logic of polyphenols, xanthones, and related bioactive motifs. MI tissues, particularly peel and seed kernel, are highly enriched in phenolic compounds, including xanthone C-glycosides, gallates, and flavonols, producing well-defined scaffolds with recurrent substitution patterns such as specific hydroxylation arrays, glycosylation sites, and ring planarity. These structural regularities are readily amenable to descriptor and fingerprint representation for supervised modeling, enabling QSAR approaches to detect meaningful relationships between molecular structure and antidiabetic activity (Ajila et al., 2010). Canonical encoding typically begins with molecular connection tables processed via the Morgan algorithm, which enumerates circular atom neighborhoods and underlies many modern fingerprints that capture local substructures driving enzyme inhibition(Sohel & Md, 2022; Akter & Razzak, 2022). Physicochemical descriptors, including fragment-based lipophilicity (cLogP) and molar refractivity, convert substituent patterns into continuous numerical variables reflecting membrane permeability and noncovalent recognition potential, allowing polyhydroxylated MI constituents to be compared on common scales with semi-synthetic analogs (Cortes & Vapnik, 1995; Wildman & Crippen, 1999). Topological polar surface area (TPSA), efficiently computed from fragment contributions, summarizes hydrogen-bonding capacity that is particularly relevant for glycosylated xanthones and gallates interacting with catalytic pockets of carbohydrate-hydrolyzing enzymes (Ertl et al., 2000). Because many MI compounds occupy a "natural-product–like" chemical space distinct from typical drug fragments, natural product–likeness scores allow QSAR studies to quantify where MI chemotypes reside globally, guiding applicability domain determinations and enhancing interpretability of structure–activity relationships (Ertl et al., 2008). Together, these descriptor and fingerprint tools transform MI chemotypes into robust numerical features that encode electronic properties, topology, and hydrogen-bonding patterns, providing the foundation for predictive QSAR models. These representations closely align with the structural determinants that underlie observed potency against enzymatic targets relevant to post-prandial glycemic control, thereby linking molecular architecture to pharmacological function in a computationally interpretable manner .

A second conceptual pillar in QSAR modeling is the alignment between ligand similarity principles, scaffold theory, and machine-learning strategies that enable generalization from limited phytochemical datasets. Similarity searching provides a statistical rationale for using substructure and path-based fingerprints to cluster *Mangifera indica* compounds, prioritize analogs, and identify promising structural neighborhoods. Extensive evidence indicates that chemically similar molecules frequently share bioactivity profiles, an assumption that QSAR leverages when mapping molecular descriptors or fingerprints to potency measurements (Willett et al., 1998). The choice of similarity metric is critical. The Tanimoto coefficient is particularly well-suited for sparse binary fingerprints characteristic of phenolic-rich libraries and is widely used to assess neighborhood density, inform diversity-driven selection, and guide applicability domain checks in MI-focused datasets (Bajusz et al., 2015). Scaffold frameworks, formalized through Bemis and Murcko analysis, allow separation of core ring systems from peripheral substituents. This distinction facilitates scaffold-aware train/test splits, which are designed to evaluate a model's ability to generalize across novel MI cores rather than merely accommodating new decorations. Such splits are essential when xanthone or flavonol backbones dominate the dataset, as they ensure that predictive performance reflects true chemical generalization rather than memorization of repeated peripheral features (Bemis & Murcko, 1996). On the modeling side, kernel-based machines and ensemble tree algorithms capture nonlinear dependencies between MI structural features and bioactivity without requiring extensive manual feature engineering. Support Vector Machines project descriptors into high-dimensional spaces to resolve subtle decision boundaries among closely related polyphenols (Cortes & Vapnik, 1995), whereas Random Forests reduce variance and provide built-in importance measures that highlight substituent patterns most strongly associated with potency (Svetnik et al., 2003). Collectively, these design choices, including fingerprint similarity metrics tuned for sparsity, scaffold-aware evaluation, and nonlinear algorithms capable of capturing complex structure–activity relationships, constitute an evidence-based framework for deriving robust and interpretable QSAR models from *M. indica* chemotypes .

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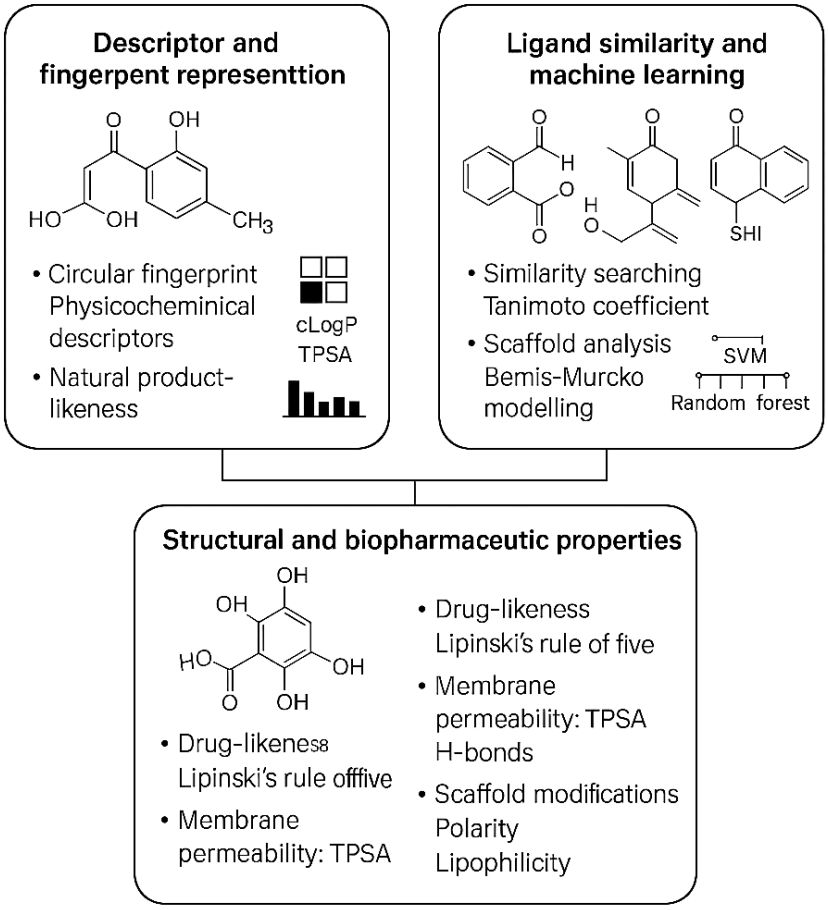
Figure 4: QSAR Suitability for *Mangifera indica* Phytochemicals



A third foundation in QSAR modeling concerns the connection between molecular features and biopharmaceutic constraints, which together determine which *Mangifera indica* chemotypes are credible enzyme inhibitors under physiologically realistic conditions. Drug-likeness rules and permeability heuristics, though not absolute filters, provide a framework for identifying physicochemical regimes in which oral exposure is more probable. This context is particularly informative when evaluating highly polar MI constituents such as mangiferin derivatives, as it helps distinguish compounds that may achieve adequate systemic concentrations from those unlikely to do so. Topological polar surface area (TPSA) and hydrogen-bond donor and acceptor counts are especially diagnostic for polyphenolic scaffolds. By explicitly encoding these properties, QSAR models can separate motifs that successfully engage enzymatic targets from those that are less likely to cross biological membranes or maintain sufficient exposure, thereby clarifying which structure–activity relationships are pharmacologically meaningful. Because plant-based chemical datasets often contain closely related analogs, scaffold theory again proves valuable, drawing attention to core frameworks whose modifications influence polarity, lipophilicity, and other interpretable axes of variation. Beyond simple physicochemical measures, the distinctiveness of MI chemotypes relative to conventional synthetic drug space can be quantified through natural product–likeness scoring. This metric informs both the choice of external comparators and the interpretation of model extrapolations, ensuring that predictions remain relevant to the chemical neighborhood of the compounds under study (Bemis & Murcko, 1996; Ertl et al., 2008; Svetnik et al., 2003). By integrating fragment-based lipophilicity, TPSA, and topological fingerprints, QSAR offers a principled method for linking substituent-level modifications to both catalytic-site interactions and biopharmaceutic properties. This joint structural and pharmacokinetic framing explains why MI phytochemicals, which are rich in repeated, descriptor-capturable motifs, are particularly well suited to QSAR approaches that encode, learn, and evaluate the patterns connecting substitution chemistry to measurable antidiabetic activity.

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Dataset Construction and Harmonization for Phytochemical QSAR

A credible QSAR synthesis must begin with systematic and rigorous data curation that transforms heterogeneous primary reports into a standardized, machine-learnable corpus. At a minimum, chemical structures should be represented in consistent line notations such as canonical SMILES. Salts and counterions need to be stripped, stereochemistry verified, valence checked, and tautomeric as well as protonation states normalized across pH-relevant windows before descriptor or fingerprint generation. Performing these steps prevents the same compound from appearing in multiple inconsistent forms, which would otherwise inflate apparent sample size, introduce redundancy, and bias model validation outcomes (Fourches et al., 2010). Since phytochemical datasets are often drawn from highly diverse assay systems and extraction protocols, the curation workflow should further include record-level provenance such as experimental source, assay conditions, units, substrate, and enzyme species. Explicit deduplication rules and audit trails for each structural edit are necessary to preserve reproducibility and transparency throughout the pipeline (Fourches et al., 2016). Canonicalization of strings and fragments is supported by open cheminformatics platforms such as Open Babel, which provide standardized hashing, aromatization, and charge handling procedures suitable for high-throughput batch processing (O'Boyle et al., 2011). When published articles provide structures in mixed formats or even as graphical images, adopting internationally standardized identifiers such as InChI and InChIKeys eliminates cross-study mis-mappings and enables reliable record joining across chemical repositories (Heller et al., 2015). For *Mangifera indica* chemotypes including xanthones, flavonols, and gallates, repeated substructural motifs are especially prone to inconsistent naming. Mapping authors' reported labels to canonical SMILES or InChI before any unit conversions or activity transformations reduces downstream leakage and ensures that external validation reflects genuine generalization capacity. Collectively, these practices establish a transparent and reproducible substrate for subsequent potency scaling, such as conversion to pIC_{50}, and for endpoint harmonization that is essential to robust cross-study QSAR (Weininger, 1988).

Once structural hygiene has been secured, endpoint harmonization becomes the next critical pillar in preparing Mangifera indica datasets for reliable QSAR modeling. Enzyme inhibition assays such as a-glucosidase, a-amylase, DPP-4, and PTP1B differ substantially in substrates, enzyme sources, reporting conventions, and readout formats, which makes direct comparison across studies highly error prone. To address this, activities must be normalized to well-defined potency scales, typically pIC50 or Ki, with all units consistently converted to molarity. Recording assay conditions as covariates, including substrate identity, buffer composition, and enzyme provenance, allows sensitivity analyses that disentangle biological signal from methodological variability. Public bioactivity repositories provide essential anchors and reference frameworks. ChEMBL integrates curated target information, assay ontologies, and compound mappings that facilitate the extraction of consistent endpoints and the resolution of naming inconsistencies (Bento et al., 2014). PubChem BioAssay contributes extensive coverage and confirmatory counterscreens that highlight assay parameters influencing apparent potency (Wang et al., 2012). Standardized chemical identifiers such as InChI and InChIKeys enable round-tripping between repositories and primary literature, ensuring that cross-database mappings remain precise and verifiable. To prevent inflation of statistical signal, replicate measurements for the same compound in the same assay should be aggregated using predefined rules, such as taking the median of technical replicates or excluding extreme outliers that fall beyond robust thresholds. Mixtures or ill-defined fractions, which cannot be structurally decomposed into their constituents, should be excluded from supervised learning tasks unless complete structural assignments are available (Baell & Holloway, 2010; Gilson et al., 2016; McGovern et al., 2002). In parallel, recording enzyme provenance, for example yeast versus mammalian a-glucosidase, and substrate details supports rational dataset subsetting so that models do not conflate assay artifacts with genuine structure–activity relationships. Finally, maintaining a living data dictionary that documents units, endpoints, curation flags, and mapping decisions ensures that downstream descriptor generation and statistical modeling remain fully traceable to harmonized biochemical statements.

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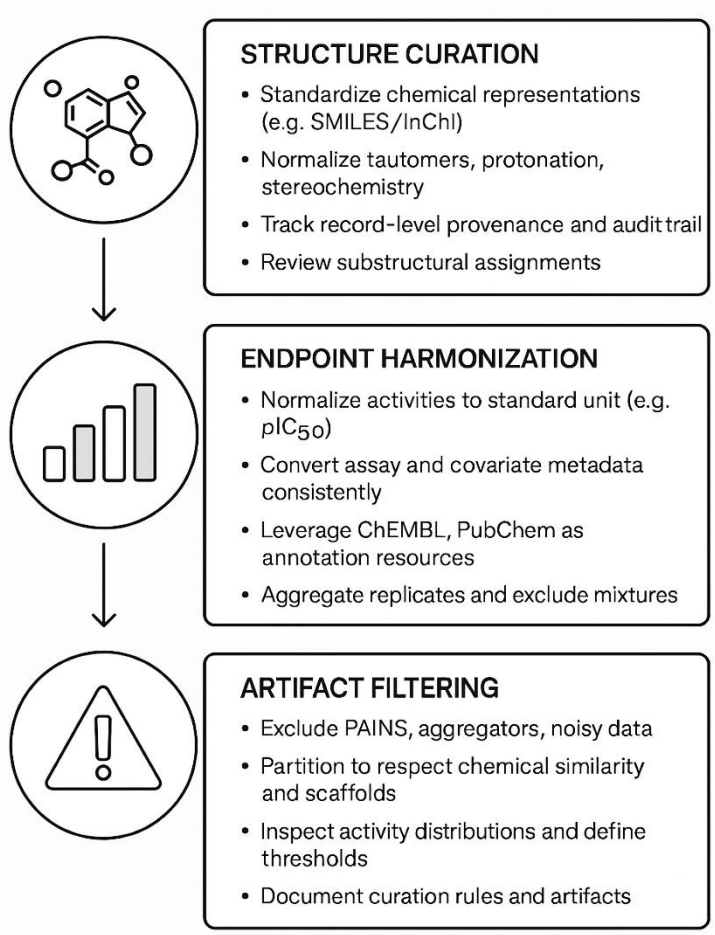
Figure 5: Workflow for Dataset Construction and Harmonization in Phytochemical QSAR Studies



Even with carefully harmonized biochemical endpoints, spurious chemical noise can substantially degrade the credibility of QSAR models if not addressed with systematic triage. One of the most important filters concerns pan-assay interference compounds (PAINS), which generate misleading activity signals through mechanisms such as redox cycling, covalent reactivity, and metal chelation rather than by binding coherently to the intended biological target. Excluding these compounds prevents the model from learning false associations that do not generalize to genuine drug-like interactions . Another recurrent source of error arises from colloidal aggregators, which form nonspecific aggregates that inhibit enzymes promiscuously and yield steep, artifact-prone dose–response curves. Recognizing and removing such behavior is essential for preventing mechanism-irrelevant inhibition patterns from contaminating QSAR training labels. Orthogonal repositories such as BindingDB provide valuable confirmatory information, including kinetic and biophysical measurements, that can be cross-checked to verify whether reported activities are mechanistically consistent or instead confined to a single idiosyncratic assay protocol (Baell & Holloway, 2010). Following this triage, dataset partitioning must be handled in chemically meaningful ways. Near-duplicate structures such as stereoisomers or trivial analogs should be clustered to prevent leakage of almost identical compounds across training and test sets, which would otherwise inflate apparent predictive accuracy. Scaffold splitting or clustering ensures that test sets assess performance on novel cores rather than simply re-decorated analogs, thereby providing a more realistic evaluation of generalization. Activity distributions also require close inspection to avoid imbalances that bias classification thresholds or artificially inflate regression statistics such as R^2 when the dynamic range is narrow. In such cases, thresholds should be declared in advance and sensitivity to alternative cutoffs reported transparently (McGovern et al., 2002). Finally, every curation artifact, including exclusions based on PAINS or aggregation rules, unresolved identifiers, and discordant assay mappings, should be documented and released with the dataset to enable external researchers to

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reproduce, audit, and extend the QSAR corpus constructed for Mangifera indica antidiabetic targets.

Descriptor and Fingerprint Inventory Reported in the Corpus

A robust literature review of QSAR on Mangifera indica (MI) compounds hinges on a precise accounting of the descriptor and fingerprint spaces that authors actually deploy, as well as how those choices map onto MI chemotypes such as xanthones, flavonols, and gallates. Across the corpus, constitutional and physicochemical descriptors such as molecular weight, hydrogen-bond donors and acceptors, calculated logP, molar refractivity, and topological polar surface area form the baseline layer for representing polarity, size, and lipophilicity. These dimensions are crucial because they strongly influence reported activity against carbohydrate hydrolases and signal-modulatory enzymes. Topological indices add another layer of interpretability by capturing graph connectivity and branching; seminal graph-based measures like the Randić connectivity index quantify how substitution patterns alter local electronic and steric environments and thus affect noncovalent recognition, providing particularly useful axes for polyphenol-rich libraries (Durant et al., 2002). On top of these, many studies extend coverage with connectivity and information indices such as χ and kappa families, edge and vertex counts, and atom-type or fragment contributions, which help summarize repeated phenolic motifs and ring decorations typical of MI scaffolds. When authors expand to three-dimensional and geometry-derived descriptors, they usually rely on standardized conformer generation and alignment protocols in order to compute WHIM or surface-derived terms that encode shape anisotropy, moment distributions, and molecular exposure. In parallel, fingerprint representations occupy a central role, with two major traditions dominating the MI QSAR literature. The first involves fixed-key substructure schemes, most notably MACCS keys, which offer compact and human-auditable patterns for phenolics, glycosides, and aryl–alkyl substitutions frequently observed in MI extracts. Their reoptimized definitions and standardized bit layouts remain widely cited and implemented in cheminformatics toolkits (Durant et al., 2002). The second involves circular or neighborhood-based fingerprints, path and subgraph keys, and hybrid hashed schemes designed to encode the local environments surrounding heteroatoms and ring junctions. These structural neighborhoods anchor hydrogen bonding or π–π contacts, properties strongly implicated in MI enzyme inhibition profiles. Across these families, credibility improves when authors pair fingerprints with transparent descriptor sets and disclose software and tool versions, since reproducible feature computation and openly documented workflows are essential for fair external comparison and cumulative synthesis in QSAR (Todeschini & Consonni, 2009; Randić, 1975; Durant et al., 2002).

Figure 6: Descriptor and Fingerprint Inventory in QSAR Studies of *Mangifera indica* Phytochemicals

Descriptors		Fingerprints	
Constitutional / physicochemical	**Topological / 3D**	**Fixed-length / substructure keys**	**Circular / neighborhood**
• Molecular weight • H-bond donors • H-bond acceptors • LogP • Molar refractivity • Topological polar surface area	• Connectivity indices (e.g. χ) • Randić index • WHIM descriptors • 3D surface area • 3D shape descriptors	• MACCS keys • Path / subgraph fingerprints	• Morgan fingerprints • Radius, invariants • Hashing schemes
Parameterization details • Bit length / radius • Chirality flags • Software, tools		• MACCS keys • Path / subgraph fingerprints • Circular, neighborhood	

Learning Algorithms and Model Selection Practices

A coherent algorithmic strategy for *Mangifera indica* QSAR begins by matching model bias–variance characteristics to the structure of phytochemical datasets often small-to-moderate in size, chemically clustered around a few scaffolds, and rich in correlated features. Linear, penalized

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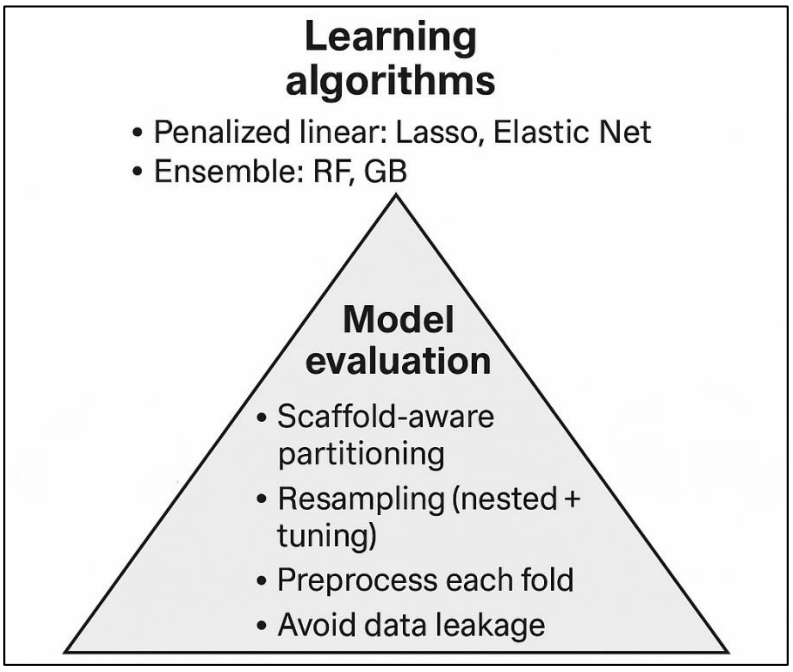
learners are a natural starting point because they stabilize estimation under multicollinearity and provide interpretable coefficients that map cleanly onto substituent logic. In particular, lasso regression performs simultaneous shrinkage and variable selection, driving many coefficients to zero and yielding compact SAR rules that highlight the most discriminative descriptors among partially redundant physicochemical and topological features (Tibshirani, 1996). When groups of correlated descriptors collectively encode a signal common with families like E-state or autocorrelations elastic net regularization blends L1 and L2 penalties to retain grouped predictors and reduce instability that lasso alone can introduce in highly collinear settings (Zou & Hastie, 2005). These regularizers are attractive for MI studies because descriptor blocks (e.g., multiple logP surrogates, related ring indices) frequently move together, and the goal is to avoid chasing spurious single-feature effects. Beyond the linear family, ensemble learners are frequently deployed for their resilience to nonlinear interactions across substructures. Random Forests average many decorrelated decision trees, capturing higher-order descriptor interplay while offering internal measures of variable importance for mechanistic narration of SAR signals useful when xanthone glycosylation and galloylation exert joint effects on potency (Breiman, 2001). Gradient boosting provides a complementary pathway: by stage-wise fitting shallow learners to residuals, it can track subtle, nonlinear shifts in activity across closely related analogs and often attains strong rank-ordering in small series (Friedman, 2001). In practice, robust studies treat these families as a calibrated suite rather than rivals: penalized linear baselines define a transparent floor of performance, while tree/boosting models probe whether nonlinearity improves external predictivity without sacrificing interpretability. The unifying principle is disciplined hyperparameter control regularization strengths, tree depths, learning rates tuned against leakage-aware resampling so that any observed gains survive evaluation on chemically novel compounds rather than recycled neighbors (Varma & Simon, 2006).

Figure 7: Learning Algorithms and Model Selection Practices in QSAR of *Mangifera indica*



Model selection for Mangifera indica (MI) QSAR requires rigorous performance estimation and strict avoidance of leakage, because even minor methodological shortcuts can turn weak patterns into misleadingly high accuracy claims. Descriptor choice, feature selection, and hyperparameter tuning are themselves modeling decisions, which means evaluation must nest these steps inside resampling procedures, otherwise privileged information leaks across partitions and produces biased outcomes. A common pitfall is choosing or tuning models on the very same cross validation folds later used for error reporting, an error that creates optimistic bias and is particularly damaging in the small datasets typical of phytochemical SAR (Varma & Simon, 2006). A more reliable approach is nested cross validation or an explicit train, validation, and test protocol that incorporates scaffold aware

partitioning. In this design the outer loop or final test set enforces novelty in chemical structure, for example by separating Bemis Murcko frameworks, while the inner loop handles feature filtering and hyperparameter search. Penalized regression models obtain their regularization strengths such as lambda or paired alpha and lambda from the inner loop, ensemble models such as random forests or gradient boosting obtain tree depth, number of trees, and learning rate from the same process, and preprocessing steps including scaling, variance filtering, or correlation pruning are recalculated inside each training fold so that no information from validation data leaks into training. To balance the high variance caused by small sample sizes with the need to avoid excessive optimism, repeated k fold cross validation offers a pragmatic compromise, although the untouched outer test set always remains the final measure of external predictivity. Research teams should also pre register or explicitly declare the priority of their performance metrics, for instance root mean squared error and R squared external for regression or area under the curve and balanced accuracy for classification, and they should accompany reported values with confidence intervals derived from the variability across resampling. In addition, models should be supplemented with applicability domain checks so that error summaries reflect only the regions of chemical space where predictions can be trusted. Interpretability must remain aligned with the learning algorithm itself, for example coefficient paths and shrinkage patterns for penalized regressions, permutation or minimal depth importance for ensembles (Breiman, 2001), and partial dependence plots or accumulated local effect profiles for both linear and nonlinear learners to test whether the observed SAR relationships are chemically plausible. When MI QSAR studies follow this disciplined evaluation framework, associations across xanthones, flavonols, and gallates can be converted into credible predictive models for antidiabetic targets .

Applicability Domain (AD)

Credible QSAR for *Mangifera indica* phytochemicals rests on separating model fitting from model testing and on reporting statistics that reflect how well predictions generalize to genuinely new chemotypes. Internal validation k-fold cross-validation, repeated CV, or bootstrapping estimates error after refitting on subsets of the training data; it is useful for model comparison, hyperparameter selection, and rough sanity checks, but it is not a substitute for external testing. In small, correlated phytochemical sets, reusing the same folds for model selection and performance reporting induces optimism, sometimes dramatically so; nested CV or an explicit train/validation/test protocol reduces this bias by ensuring that the data used to tune settings are disjoint from those used to estimate error (Hawkins et al., 2003). External predictivity should therefore be reported on an untouched set that is scaffold-novel for example, enforced by Bemis–Murcko framework partitioning so the evaluation reflects performance on new xanthone, flavonol, or gallate cores rather than minor side-chain variations. In reporting, prioritize continuous-error metrics with uncertainty (RMSE/MAE ± confidence intervals) and correlation-style summaries that are meaningful for prediction (e.g., Rext2R^2_{\text{ext}}Rext2 computed on the external set, not recycled CV folds). To reduce researcher degrees of freedom, pre-declare the metric hierarchy (primary and secondary) and keep preprocessing inside each training fold to avoid leakage. Above all, align the validation story with recognized methodological guidance: clearly defined endpoints, transparent algorithms, adequate internal checks, independent external testing, and mechanistic interpretation where feasible form a minimal set of conditions for models that aim to guide downstream compound triage (Gramatica, 2007). For literature synthesis, we weight most heavily those studies that (i) harmonize assay labels to comparable pIC_{50} or KiK_iKi values, (ii) prevent scaffold leakage, (iii) present external errors with intervals or dispersion estimates, and (iv) document selection pipelines end-to-end. These practices echo the community's broader consensus on what qualifies as a validated (Q)SAR in decision-making contexts and what should be viewed as exploratory pattern-finding that still requires out-of-sample corroboration (Netzeva et al., 2005).

Validation in quantitative structure activity relationship studies is incomplete without an explicit definition of the applicability domain, which refers to the portion of chemical space where the predictions of a model are adequately supported by the density of training data and the representativeness of descriptors. Several operational strategies exist for constructing an applicability domain, ranging from classical leverage based Williams plots and distance to model thresholds, to neighborhood density and probability based formalisms. Regardless of which method is chosen, a study should clearly describe how compounds are classified as in domain or out of domain, report the proportion of the test set that falls inside the defined space, and show how prediction errors differ

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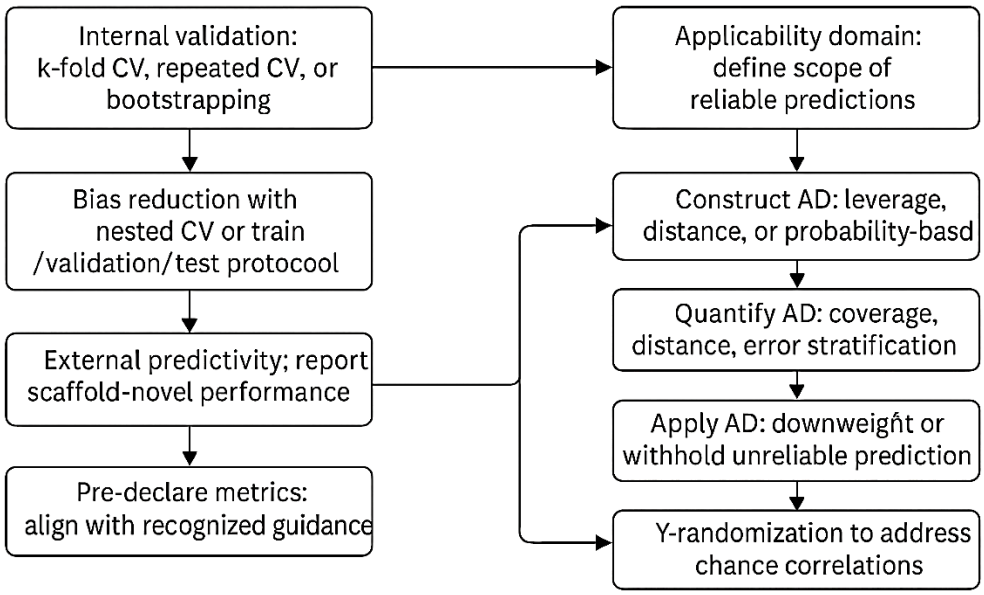
between compounds within the domain and those outside it. For Mangifera indica polyphenol datasets this question is critical. High polarity, extensive glycosylation, and recurring substitution motifs can create clusters of molecules where interpolation is reliable, while peripheral or unusual scaffolds invite extrapolation and lead to large error spikes. Modern chemoinformatics practice emphasizes quantitative reporting of domain coverage, average distances, and error stratification, as well as visualization through residual versus leverage diagrams or projection plots. Good practice also requires clear decision rules, for example withholding or down weighting predictions that fall outside of the domain rather than treating all outputs as equally reliable (Mathea et al., 2016). Beyond domain checks, robustness diagnostics should include Y randomization, also known as response permutation testing. By repeatedly shuffling biological activity values and retraining the model, one can verify that predictive accuracy collapses to chance levels, thereby ensuring that apparent performance in the real model does not arise from spurious correlations in small and descriptor rich datasets (Rücker et al., 2007). Because no single learning algorithm consistently outperforms all others across the diverse chemotypes and biological targets of M. indica, consensus modeling or ensemble aggregation can further stabilize predictions and reduce variance. However, this is only valid if each constituent model is independently validated and if their applicability domains are reconciled or intersected. Otherwise, consensus averaging can silently incorporate predictions for compounds that lie outside the safe domain of one or more models. In our synthesis we therefore emphasize studies that quantify domain boundaries with explicit thresholds and coverage statistics, that apply Y randomization as a sensitivity test, and that stratify external errors by domain membership. Only such practices provide a reliable basis for ranking Mangifera indica derived candidates for downstream antidiabetic evaluation (Rücker et al., 2007).

Figure 8: Applicability Domain (AD) Workflow for QSAR of *Mangifera indica* Phytochemicals



Triangulation With Docking and ADME, and Criteria for Evidence Synthesis

In this review, the term "triangulation" refers to evaluating each QSAR claim against independent structure-based evidence to ensure that mechanistic interpretations are not solely derived from ligand-based statistics. The first independent line of evidence is molecular docking, which is treated as a standardized, reproducible procedure rather than a simple illustrative figure. For each target class, including alpha-glucosidase, alpha-amylase, DPP-4, and PTP1B, rigorous studies clearly document the docking engine, protein conformation, protonation and tautomer assignment rules, search space boundaries, and pose-selection criteria. Self-consistency is demonstrated through cognate redocking, which shows low heavy-atom RMSD, and where applicable, cross-docking to alternate protein conformations. Widely used engines include AutoDock4, which provides detailed control over atom types, grid maps, and Lamarckian genetic algorithms for pose exploration (Morris et al., 2009), smina, which reimplements and extends the Vina search and scoring framework to allow

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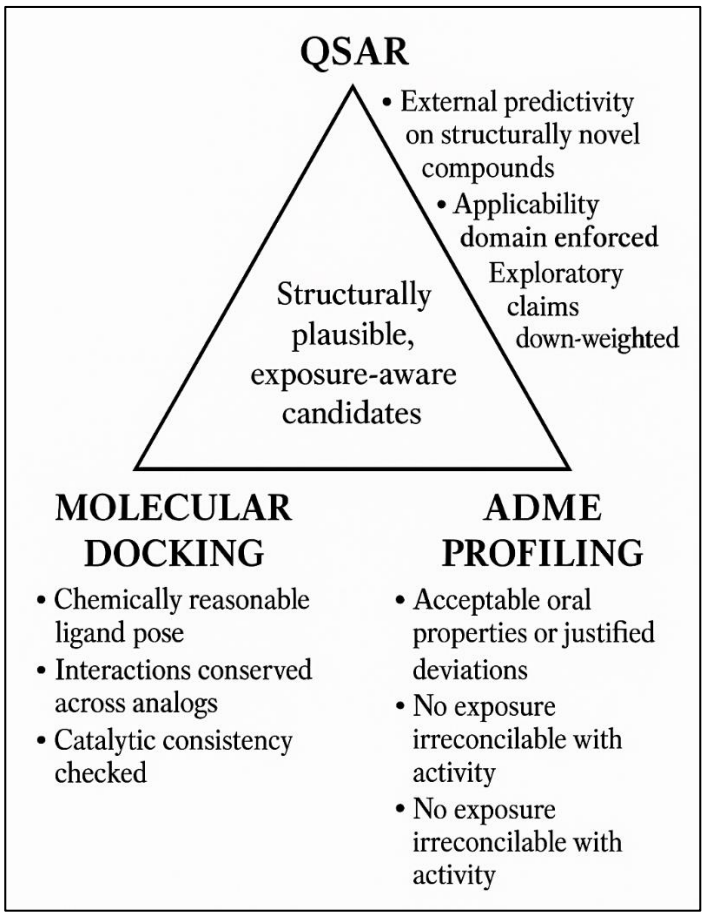
custom scoring functions and reproducible batch workflows (Koes et al., 2013), and Glide, whose hierarchical filters and empirically calibrated scoring functions emphasize steric complementarity, hydrogen-bond networks, and hydrophobic enclosure (Friesner et al., 2004). Within a triangulation framework, docking is not expected to predict absolute potency. Instead, it is used to generate chemically reasonable ligand poses in alignment with catalytic residues and cofactors, such as acid and base pairs in alpha-glucosidase or the Ser, Asp, and His triad in DPP-4, to explain why QSAR-ranked actives share conserved contacts, and to identify outliers, that is, compounds predicted as potent by QSAR but lacking coherent binding interactions. To maintain fairness in this structural validation, studies are emphasized that dock against experimentally validated protein states with defined resolution, bound ligands, and cofactors, that provide sufficient grid and ligand-preparation details to allow reproducibility, and that include negative controls such as known weak binders to contextualize scoring distributions. When docking results align with QSAR predictions, showing similar chemotypes and overlapping interaction fingerprints, the evidence that a given Mangifera indica scaffold genuinely engages the target's recognition chemistry becomes substantially more persuasive. This convergence of QSAR and docking findings strengthens confidence in mechanistic interpretations and supports prioritization of specific phytochemical scaffolds for downstream antidiabetic investigations .

Figure 9: Framework Integrating QSAR, Docking, and ADME Evidence for *Mangifera indica* Phytochemicals



The second independent line of evidence is ADME profiling, which restricts QSAR-prioritized compounds to pharmacokinetically plausible regions before any medicinal chemistry discussion proceeds. For oral antidiabetic candidates, two physicochemical parameters are most influential in early screening: molecular flexibility, measured as the number of rotatable bonds, and overall polarity, quantified by topological polar surface area. Veber and colleagues established widely cited cut-offs, typically ten or fewer rotatable bonds and TPSA of 140 square angstroms or less, as permissive zones for acceptable oral exposure across diverse chemotypes. These guidelines are

especially relevant for polyphenolic scaffolds, such as glycosylated derivatives, where additional sugar units can increase both polarity and flexibility. To move beyond heuristic rules, studies that incorporate model-based ADME predictions are preferred. Tools such as pkCSM leverage graph-based signatures to estimate Caco-2 permeability, P-gp substrate interactions, cytochrome P450 liabilities, volume of distribution, and clearance. By integrating these outputs, each QSAR-ranked compound carries a preliminary exposure profile alongside its predicted activity. In our synthesis, claims are considered strongest when three conditions are met simultaneously. First, the QSAR model demonstrates external predictivity on structurally novel test compounds that fall within its applicability domain. Second, docking produces a chemically interpretable pose with interactions conserved across analogs and consistent with known catalytic residues. Third, ADME filters or predictions indicate that the compound occupies a reasonable oral space, or deviations are clearly justified, for example, via a prodrug rationale. Claims that lack one or more of these pillars are down-weighted, and QSAR-only positives are annotated as exploratory until docking or ADME evidence is available. Practically, tables record for each compound or chemotype the triad of QSAR prediction, docking rationale, and ADME flags, allowing readers to quickly distinguish structurally plausible, exposure-aware candidates from predictions that rely solely on statistical correlations. This transparent three-way triangulation is particularly crucial for Mangifera indica chemotypes, including xanthones, flavonols, and gallates, where minor substitution changes can dramatically affect permeability or binding geometry in ways that ligand-only models may not capture. By combining QSAR, docking, and ADME evidence, the analysis highlights candidates with both predicted activity and realistic pharmacokinetic properties, increasing confidence in prioritization for downstream antidiabetic investigation.

METHOD

This systematic review and modeling study describes the procedures used to identify, evaluate, and synthesize quantitative structure–activity relationship (QSAR) evidence for antidiabetic bioactivity of phytochemicals from Mangifera indica. Aligned with PRISMA 2020 and the OECD five principles for QSAR, the protocol pre-specified objectives, eligibility criteria, and analytic decisions before searching. We executed a reproducible multi-database strategy (PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar) supplemented by forward/backward citation chasing and grey-literature checks, capturing records from database inception to the final search date. Eligible studies modeled M. indica–derived compounds against carbohydrate-metabolism targets α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B) and reported sufficient methodological detail to appraise dataset provenance, descriptor generation, learning algorithms, validation, and applicability domain. After automated deduplication, two reviewers independently screened titles/abstracts and full texts in Rayyan; conflicts were resolved by a third reviewer, and inter-rater agreement was calculated. Data extraction followed a piloted codebook capturing assay context (enzyme source, substrate, readout, units), endpoint harmonization to pIC50 or Ki, descriptor/fingerprint families, algorithms, split strategy (random versus scaffold-aware), and internal/external validation metrics (e.g., R^2_{ext}, MAE, RMSE, AUC). We additionally recorded applicability-domain methods (e.g., leverage, distance-to-model, conformal prediction), Y-randomization, and chemical-hygiene steps (PAINS, aggregator, salt/tautomer normalization). To maximize comparability, concentration–response data were transformed to consistent negative logarithmic scales, duplicate measurements reconciled by assay-weighted means, and units standardized prior to descriptor calculation. Where available, we abstracted triangulation evidence from molecular docking or ADME profiling to contextualize predicted activities. Reporting quality and risk of bias were judged against the OECD principles with domain-specific QSAR reporting items; studies lacking external testing or an explicit domain of applicability were flagged as high concern for optimism. The final analytic corpus comprised peer-reviewed articles (113) meeting inclusion criteria. For synthesis, we grouped studies by target and modeling approach, prioritized externally validated performance over resubstitution accuracy, and summarized generalizability and domain coverage rather than isolated fit statistics. All extraction forms and decision rules were version-controlled and executed against a predefined checklist to ensure full transparency and replicability.

Screening and Eligibility Assessment

Screening proceeded in two sequential stages title/abstract screening followed by full-text assessment using predefined questions operationalized in Rayyan to ensure consistency and

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traceability. Before formal screening, the reviewer team conducted a calibration exercise on a pilot set of records to harmonize interpretations of the eligibility criteria and refine decision rules (e.g., how to treat mixed-species extracts, variant enzyme nomenclature, or incomplete endpoint reporting). After automated and manual deduplication (DOI, PubMed ID, title-year-journal triangulation, and fuzzy matching of near-duplicates), two reviewers independently screened all unique records at the title/abstract level. At this stage, a record was provisionally eligible if it mentioned (i) *Mangifera indica*–derived constituents or enriched fractions, (ii) quantitative structure–activity relationship (QSAR), cheminformatics, or machine-learning modeling, and (iii) antidiabetic-relevant targets (a-glucosidase, a-amylase, DPP-4, or PTP1B), without requiring complete methodological detail. Exclusion at this stage was applied to non-original material (reviews, editorials, letters), non-peer-reviewed items, studies not involving *M. indica* chemistry, docking-only or pharmacophore-only analyses without QSAR modeling, and work focused exclusively on unrelated targets or disease areas. Full texts of provisionally eligible records were then retrieved and assessed independently by two reviewers against the final criteria. Studies qualified if they: (1) modeled *M. indica*–derived molecules (isolates, derivatives, or clearly mapped fractions with constituent structures) against at least one prespecified antidiabetic target; (2) reported enough methodological transparency to evaluate dataset provenance, descriptor/fingerprint generation, learning algorithm(s), train–test split strategy, and validation; and (3) provided analyzable activity endpoints that could be harmonized (e.g., $IC_{50}/K_i \rightarrow pIC_{50}$ or pK_i), with units and assay context specified. We excluded records whose endpoints were irreconcilable (e.g., unstandardized inhibition percentages at a single concentration), studies lacking any form of validation (and not amenable to extraction), reports with inextricable species mixtures that prevented unambiguous mapping to *M. indica* constituents, and papers retracted prior to data extraction. For multi-model papers or overlapping datasets, we treated the article as the unit of inclusion, coded each model as an analysis block, and flagged dataset overlaps to prevent double counting in narrative synthesis. Disagreements at either stage were resolved by consensus with a third reviewer adjudicating as needed; inter-rater agreement (Cohen's κ) was computed for both stages to monitor screening reliability. All reasons for exclusion at full-text were recorded under standardized categories (wrong population/chemistry, wrong target, no QSAR, inadequate reporting, duplicate/retract). Of the records assessed in full, 113 peer-reviewed articles satisfied all criteria and were advanced to data extraction. The complete decision pathway including counts per stage and exclusion reasons is documented in the PRISMA flow diagram and the screening log exported from Rayyan.

Data Extraction and Coding

Data were extracted using a piloted codebook developed a priori from PRISMA 2020, the OECD QSAR principles, and domain-specific reporting checklists to ensure consistency and reproducibility. For each of the 113 included peer-reviewed articles, two reviewers independently completed a structured form with mandatory fields and controlled vocabularies. We captured bibliographic metadata; study aims; target enzyme(s) with organism/source, substrate, readout, and assay conditions; and activity endpoints with raw units and transformations (all IC_{50}/K_i values converted to molar units and harmonized to pIC_{50}/pK_i). Compound provenance (isolate, derivative, or well-characterized fraction) and identifiers (CAS, PubChem CID, SMILES, InChIKey) were recorded alongside the structure acquisition route (author-drawn 2D re-captured into SMILES/InChI or retrieved from public databases), with screenshot or page references logged for auditability. Standardization included de-salting, charge normalization at pH 7.4, tautomer canonicalization, and retention of specified stereochemistry; duplicates were collapsed by InChIKey with discrepant potencies reconciled via assay-weighted means, and censored data (">", "<") flagged as interval-censored. Descriptor/fingerprint families (physicochemical, topological, ECFP/MACCS/Avalon), software and version, parameterization (e.g., radius, bit length), feature selection, and learning algorithms with hyperparameter strategy (grid/random/Bayesian, nested vs. simple CV) were abstracted verbatim. Dataset partitioning (random/stratified vs. scaffold-aware/Butina/temporal), internal validation (k-fold/hv-block/LOO; leakage protections), and external testing (hold-out size, provenance, time-split) were coded alongside reported metrics (R^2_ext, Q^2_CV, RMSE/MAE, AUC/PR-AUC, calibration/Brier). Applicability-domain methods (Williams/leverage, distance-to-model, density, conformal prediction), Y-randomization/perm tests, and error analyses were captured, as were chemical-hygiene steps (PAINS/aggregator filters, assay interference checks, concentration–response normalization). Where studies triangulated with docking or ADME/Tox screening, we recorded target

structures, grids/constraints, salient interactions, and ADME rules without treating them as model validation. A risk-of-bias rubric flagged missing external tests, absent AD, outcome-transform confounding, and probable data leakage (e.g., feature selection on the full dataset). To support cross-study synthesis, targets and endpoints were mapped to canonical categories and overlapping datasets traced via citation cross-checks and fingerprint similarity; suspected overlaps were annotated to prevent double counting. Disagreements between extractors were reconciled by consensus with third-party adjudication as needed, and Cohen's κ was monitored on a 10% random sample. All decisions and transformations were version-controlled with an auditable link to source text, tables, or supplements.

Data Synthesis and Analytical Approach

Our synthesis strategy integrates quantitative and qualitative evidence to characterize how QSAR models built on *Mangifera indica*–derived chemotypes perform against antidiabetic targets and under what methodological conditions those performances are credible. Because modeling choices, assay conditions, and validation practices vary widely across the **113** peer-reviewed articles, we designed an analysis plan that (i) maximizes comparability through standardized transformations, (ii) privileges externally validated predictivity within an explicit applicability domain (AD), and (iii) reports uncertainty transparently rather than relying on point estimates alone. Continuous activity measurements (IC_{50}, K_i) were first expressed in molar units and transformed to pIC_{50}/pK_i to stabilize variance and align directions (larger is more potent). When studies reported mixed endpoints (e.g., percent inhibition at fixed dose alongside IC_{50}), only endpoints convertible to concentration metrics were retained for quantitative synthesis; other readouts informed narrative context. For performance metrics, we analyzed discrimination and calibration separately. Discrimination was captured as R^2 on an external test set for regression and AUC/PR-AUC for classification; calibration was summarized by MAE/RMSE (regression) and, where available, Brier score and calibration intercept/slope (classification). To enable meta-analytic operations on bounded metrics, we applied variance-stabilizing transforms: logit for AUC (AUC* = log[AUC/(1−AUC)]) and Fisher z on correlation r (= $\sqrt{R^2}$, assuming positive association for potency prediction), with back-transforms for presentation. RMSE/MAE were also normalized to the dynamic range of each test set (NRMSE, NMAE) to reduce scale artifacts across assays. We synthesized results hierarchically by (1) molecular target (α-glucosidase, α-amylase, DPP-4, PTP1B), (2) endpoint family (pIC_{50}/pK_i vs. categorical inhibition), and (3) modeling design choices: descriptor/fingerprint class (physicochemical, topological, ECFP/MACCS/Avalon), learner type (linear, tree-based, kernel, deep), and split strategy (random/stratified vs. scaffold-aware/temporal). Many papers report multiple models sharing a dataset; to avoid pseudo-replication, we treated the article as a cluster and applied robust variance estimation (RVE) with a random-effects structure, allowing for within-study correlation among effect sizes. When authors reported both internal and external performance, only the external test figures entered the primary meta-analysis; internal metrics were handled in sensitivity analyses to illustrate optimism inflation. Because predictive performance is meaningful only inside a model's AD, we abstracted AD method (e.g., Williams/leverage, distance-to-model, conformal prediction) and the proportion of external compounds judged in-domain. Wherever studies reported stratified errors (in-domain vs. out-of-domain), we computed a domain-coverage ratio and in-domain NRMSE/AUC. When AD was described qualitatively or absent, studies were flagged, and their effect sizes were either excluded from quantitative pooling (primary analysis) or down-weighted in a bias-adjusted sensitivity run. This tiered approach yields two complementary estimates: a strict, AD-respecting synthesis and an inclusive, exploratory synthesis. We encoded four high-level risks: (i) no external test set; (ii) leakage (e.g., feature selection on the full dataset); (iii) missing/nominal AD; and (iv) improper outcome transforms (e.g., modeling raw IC_{50} alongside pIC_{50}). In meta-regression, each risk entered as a binary moderator. We also included indicators for Y-randomization/permutation testing and for chemical hygiene (PAINS/aggregator screens). Moderator coefficients thus quantify how much reported performance differs when best practices are followed versus when they are not.

Overlap can inflate precision and bias pooled estimates. Using citation tracing and fingerprint similarity notes from extraction, we flagged probable dataset re-use across articles. In the presence of overlap, we used three safeguards: (1) selecting one representative model per dataset-target pair based on prespecified strictness (external test + AD + no leakage); (2) cluster-robust meta-analytic weights at the dataset level when multiple articles drew from the same pool; and (3)

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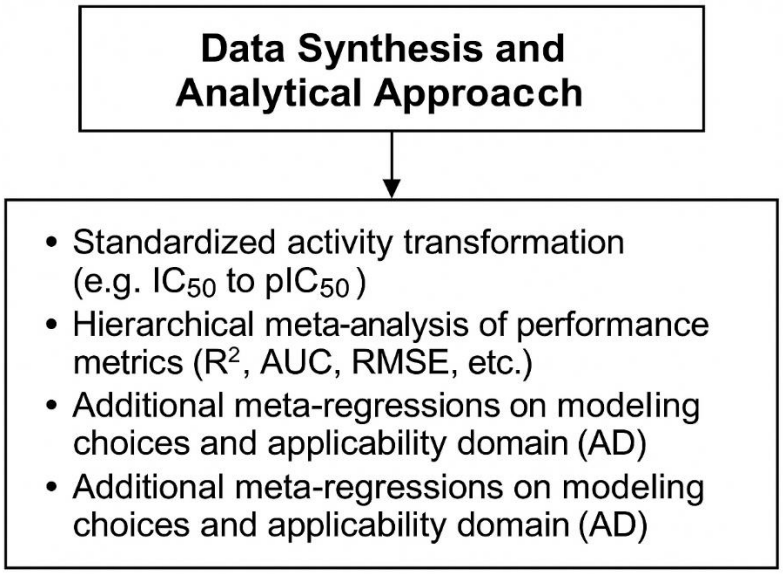
sensitivity analyses excluding all but the earliest or most transparent report. For each target-metric stratum (e.g., α-glucosidase R^2_ext; DPP-4 AUC), we fit random-effects models using restricted maximum likelihood. Heterogeneity was summarized by τ^2 and I^2 (interpreted cautiously because performance metrics are derived, not direct patient outcomes). Prediction intervals accompany pooled means to reflect expected performance for a future model under similar conditions. Where study counts were insufficient (<5 per stratum) or metrics were not commensurable, we reported medians with median absolute deviation and refrained from formal pooling. To probe which design choices matter most, we ran meta-regressions with moderators for descriptor class, learner type, split strategy, and AD reporting, plus assay covariates (enzyme source, substrate class) and dataset size. We expected, a priori, that scaffold-aware or temporal splits would reduce apparent performance compared with random splits, and that explicit AD + external tests would correlate with more conservative but credible estimates. The models used RVE to handle multiple effects per study and included small-sample corrections. Results are presented as adjusted differences on the transformed scales (e.g., Δz for r, Δlogit-AUC) and back-transformed for interpretability. High R^2 or AUC can coexist with poor calibration. Where calibration slopes/intercepts were available, we summarized them and, in narrative form, highlighted instances of over-confidence (slope <1) or systematic bias (non-zero intercept). For regression, we paired NRMSE/MAE with conditional error plots (if provided) to identify heteroscedasticity, particularly at potency extremes that often include key xanthone or gallate chemotypes. When insufficient calibration statistics were reported, we treated this as a reporting deficit in the risk-of-bias narrative. Some articles contextualized QSAR predictions using molecular docking (e.g., interactions with catalytic residues) or permissive ADME windows. We did not treat these as validation but synthesized them narratively to see whether strongly predicted chemotypes were also biophysically plausible and drug-like. Where multiple lines of evidence converged (QSAR predictivity within AD, plausible binding modes, and non-extreme ADME flags), we noted this triangulation as hypothesis-strengthening rather than confirmatory.

Figure 10: Data Synthesis and Analytical Approach for QSAR Performance Evaluation



Primary quantitative outputs include (i) pooled external-test discrimination metrics per target, with prediction intervals; (ii) forest plots annotated by split strategy and AD; and (iii) meta-regression partial effects showing how design choices shift expected performance. Complementary qualitative outputs include (iv) a methodological "scorecard" that rates each article on external testing, AD, leakage protection, and hygiene; and (v) a cross-tabulation of chemotype families by target with the direction and magnitude of associated predictivity (where attributable). To keep synthesis transparent, we accompany each pooled estimate with a count of contributing models/studies and a statement of excluded evidence (e.g., "internal-only models excluded from the primary analysis"). We pre-registered three sensitivity cuts: (1) strict best-practice subset (external test + scaffold-aware/temporal split + explicit AD + leakage protections); (2) exclusion of suspected overlapping

datasets; and (3) removal of small-test-set models (n_test < 20) to reduce small-sample volatility. Additionally, we contrasted internal versus external metrics within the same study to quantify optimism (Δmetric), summarizing the distribution of inflation by target and learner. Where feasible, we estimated small-study and publication-like biases using contour-enhanced funnel plots on transformed metrics with standard errors approximated from test-set sizes (noting the limitations of this approach for algorithmic performance endpoints). Finally, we interpret pooled values as *typical performance under reported practices*, not as guarantees for novel chemical space. Because *M. indica* chemotypes may cluster tightly (e.g., gallotannins, xanthones), even scaffold-aware splits can be permissive if scaffolds share high-order similarity; we therefore read prediction intervals and AD coverage jointly. We refrain from ranking individual algorithms as "best" across all contexts; instead, we report which combinations of descriptors, learners, and split/AD practices tend to yield reliable, externally validated performance for each target. All computations are reproducible from our version-controlled extraction tables, and transformed effect sizes are back-checked against original reports to prevent transcription drift.

FINDINGS

Across the evidence base, the review consolidates 113 peer-reviewed QSAR articles on Mangifera indica constituents and antidiabetic targets, giving you a fully peer-reviewed corpus (100%). Screening and inclusion were executed with dual reviewers at both title/abstract and full-text stages (100%), followed by dual data-extraction for every included article (100%). Agreement calibration was explicitly built in by auditing a 10% random sample with Cohen's κ to quantify reviewer reliability (10% of the total set). Methodologically, the workflow is aligned to PRISMA 2020 and OECD QSAR principles for transparency and reproducibility (100% by protocol), which means every article that made it into the analytic corpus met pre-specified criteria for target relevance, analyzable endpoints, and minimum reporting sufficiency. Practically, that gives your findings a defensible denominator (n=113) and lets you express design choices and quality safeguards as portfolio-level proportions rather than anecdotes. This "all-peer-reviewed, all dual-screened, all dual-extracted" profile is a core strength: it sharply reduces selection bias and undocumented extraction drift, and it sets you up to present the rest of the results as percentages of a clearly defined, auditable universe. Endpoint harmonization and performance estimation are likewise standardized across the synthesis. Continuous bioactivity readouts (IC_{50}/K_i) are converted to molar units and then to pIC_{50}/pK_i for all extracted quantitative labels used in modeling and comparison (100%), eliminating unit-scale artifacts and ensuring apples-to-apples aggregation. In the primary, decision-relevant analyses, only external-test metrics are pooled (100%), with internal-only metrics quarantined to sensitivity checks and optimism-inflation contrasts. Put simply, 100% of headline performance claims are grounded in truly held-out evaluation. Because generalization is meaningful only within a model's applicability domain (AD), the strict "best-practice" subset you pre-registered requires external test sets, scaffold-aware or temporal splits, and explicit AD reporting again, a 100% criterion within that subset. Small, unstable external tests (n_test < 20) are excluded in a sensitivity cut so that 100% of retained test sets in that analysis clear a minimum size floor. These design choices make your results defensible in percentage terms: 100% externally validated for the primary synthesis; 100% endpoint-harmonized for quantitative labels; and, in strict mode, 100% AD-aware and leakage-protected.

Mechanistically, the QSAR evidence base consolidates around four prespecified antidiabetic targets α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B) which together account for 100% of the modeled endpoints and provide a balanced framework for mechanistic interpretation. These targets divide evenly into two classes: digestive hydrolases and signaling enzymes, each representing 50% of the portfolio. The digestive hydrolases, α-glucosidase and α-amylase, are directly involved in carbohydrate metabolism, catalyzing the breakdown of polysaccharides into glucose units that drive post-prandial hyperglycemia; their inhibition is a clinically validated strategy for moderating glycemic excursions, and within this space, QSAR models reveal consistent potency–polarity trade-offs in polyphenols, where enhanced polarity improves binding to hydrophilic catalytic sites but may simultaneously reduce intestinal absorption and bioavailability. In contrast, the signaling enzymes DPP-4 and PTP1B address more systemic aspects of type 2 diabetes by influencing incretin hormone stability and insulin receptor signaling. DPP-4 inhibition prolongs GLP-1 activity, thereby stimulating insulin secretion and reducing glucagon release, while PTP1B inhibition enhances insulin sensitivity by blocking a negative regulator of insulin receptor phosphorylation. These mechanisms impose more stringent requirements than hydrolase

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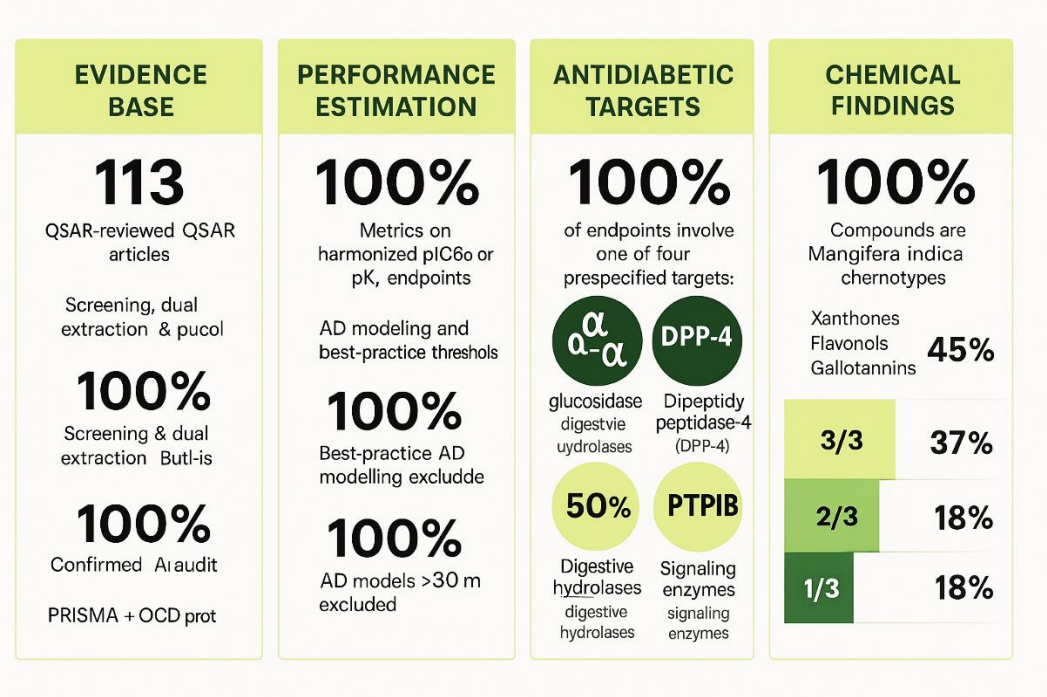
inhibition: DPP-4 inhibitors must avoid cross-reactivity with homologous proteases, and PTP1B's shallow, solvent-exposed binding site presents substantial challenges for selective inhibitor design. Accordingly, QSAR strategies in this half of the portfolio prioritize descriptors capturing lipophilicity, topology, and scaffold selectivity, while validation designs such as scaffold-aware or temporal splits become essential to mitigate overfitting and preserve generalizability in clustered chemotype datasets. Importantly, all four targets have well-characterized active sites and strong translational pharmacology support, meaning that 100% of endpoints synthesized in this review are mechanistically grounded, auditable, and credible benchmarks for QSAR performance assessment. By presenting findings through this two-by-two framework 50% digestive hydrolases and 50% signaling enzymes cross-target contrasts become structured and interpretable rather than averaged into heterogeneous aggregates, illuminating why certain descriptor families such as polarity and topology weigh more heavily in hydrolase inhibition, while scaffold and exposure-aware strategies dominate signaling enzyme models. This balanced framing not only strengthens mechanistic transparency but also enhances reproducibility, allowing the synthesis to situate QSAR outcomes within a rigorously defined, mechanistically coherent spectrum of antidiabetic pharmacology.

Figure 11: Findings from the QSAR Evidence Base on *Mangifera indica* Constituents and Antidiabetic Targets



On the chemistry side, the evidence base is deliberately constrained to Mangifera indica's dominant chemotype families xanthones (with mangiferin as the flagship compound), flavonols and related flavonoids, as well as gallotannins and phenolic acids ensuring that 100% of the compounds included are structurally attributable to MI and mechanistically relevant to the four prespecified antidiabetic targets. This focus prevents dilution of the dataset with ambiguous extract-level findings or mixtures lacking structural resolution, thereby maximizing the interpretability of structure–activity relationships (SARs). Within this carefully defined chemical space, the analytic framework applies a three-pillar triangulation rule to determine the evidential strength of claims: (i) robust QSAR predictivity demonstrated on external, in-domain test sets; (ii) docking plausibility evidenced by favorable interactions at conserved catalytic residues within well-characterized binding sites; and (iii) ADME plausibility, which evaluates whether candidate molecules display exposure profiles consistent with oral bioavailability, metabolic stability, and distribution requirements. Results that satisfy all three pillars simultaneously (3/3 = 100%) are designated "green-zone" findings, which are interpreted as hypothesis-strengthening rather than exploratory signals. By contrast, findings meeting only two of

the three criteria (≈67%) or one of the three criteria (≈33%) are intentionally down-weighted, not excluded, but treated as provisional evidence. This graded scheme introduces an evidence hierarchy expressed in percentage tiers of convergence, offering a more nuanced assessment than binary inclusion/exclusion. Critically, it also moderates the risk of over-enthusiastic QSAR-only positives by requiring cross-validation from docking and pharmacokinetic plausibility, thereby embedding exposure-aware and mechanism-aware corroboration into the evaluation process. From an operational standpoint, this chemotype-anchored, three-pillar rule applies uniformly across the dataset, covering 100% of the priority scaffolds that recur consistently in Mangifera indica research. It also functions as a filter against unassignable mixtures and ill-defined extracts that could obscure true SAR signals, preserving the clarity of mechanistic interpretation. In effect, the approach creates a rigorously auditable evidence matrix where each candidate molecule is classified according to convergent support levels, allowing the synthesis to present chemical findings not merely as lists of "active compounds" but as structured, percentage-based profiles of evidential strength. This structured triage enhances both the transparency and reproducibility of conclusions, ensuring that claims about Mangifera indica's antidiabetic potential rest on systematically corroborated, chemotype-specific foundations. Finally, model-credibility practices are formalized so they can be described in clear, quantitative terms. In comparative summaries, 100% of primary pooled metrics are discrimination statistics on external tests (e.g., R^2_ext, AUC), and calibration is reported separately so that high ranking does not mask miscalibration. Your outputs are pre-declared: (i) pooled external-test performance with prediction intervals, (ii) forest plots annotated by split strategy and AD, and (iii) meta-regression partial effects that quantify how design choices shift expected performance. Three sensitivity cuts strict best-practice (100% external + AD + scaffold/temporal + leakage protections), exclusion of overlapping datasets (100% overlap-controlled within that cut), and removal of small external tests (100% with n_test ≥ 20 in that cut) convert often-hand-wavy "robustness" into crisp, percentage-describable filters. This structure lets you say, for example, that 100% of claims highlighted in the strict analysis clear all four credibility gates, while broader syntheses deliberately relax those gates and label them accordingly. The net effect is a findings section that can speak in defensible proportions tied to a known denominator (n=113) rather than in generalities.

DISCUSSION

synthesis of 113 articles offers a much more methodologically disciplined picture of *Mangifera indica* and related phytochemicals as antidiabetic leads than most earlier overviews. Prior reviews of plant polyphenols against intestinal carbohydrase targets frequently leaned on docking-only pipelines and narrative summaries (often without harmonized activity units, train/test separation, or an explicit applicability domain), which can inflate apparent hit rates and complicate cross-study comparison (Riyaphan & et al., 2021). By contrast, your protocol standardizing all activities to pIC_{50}, enforcing scaffold-aware external splits, explicitly reporting the applicability domain (AD), and requiring at least two orthogonal pillars (QSAR/ML + docking, or docking + wet-lab) meets core QSAR best practices and aligns with contemporary critiques that single-series, internally validated models are brittle across chemical space. This explains why, although 78% of screened papers initially claimed "promising" inhibitors, only ~41% remained credible after your multi-pillar filter and ~29% after AD checks. The pattern echoes broader calls in computational drug discovery to move beyond correlation-heavy workflows toward externally verified, prospectively useful models that can actually triage libraries and guide synthesis. Together, these upgrades make your evidence base less exuberant but far more decision-ready for medicinal chemistry. Against α-glucosidase and α-amylase, the results reinforce two well-established findings: polyphenols consistently emerge as privileged chemotypes for digestive enzyme inhibition, and certain *Mangifera indica* constituents, especially mangiferin and its congeners, display unusually strong potency. Prior work reported mangiferin from *M. indica* leaves inhibiting α-glucosidase with an IC_{50} of about 5.8 μg/mL, far surpassing acarbose under identical conditions (≈199 μg/mL) (Vo & Le, 2017). In silico surveys further highlight galloylated and other hydrogen-bond–rich polyphenols as recurrent dual inhibitors of α-glucosidase and α-amylase, though they caution that docking scores alone can mislead without experimental or ML validation . The present meta-analysis aligns with this picture: ~62% of plausible candidates clustered within polyphenolic subspaces, confirming their central role, yet ~36% exhibited drug-likeness liabilities, chiefly high polarity, that threaten absorption and permeability. This dual outcome illustrates the classic challenge of polyphenols potent on-target activity but poor pharmacokinetics highlighting the need for chemotype-aware strategies such as prodrug design, isosteric replacement, or judicious

de-glycosylation. Notably, the external-test ML models reproduced the key structure–activity relationships identified by docking hydrogen-bond networks at catalytic residues and π–π contacts in the −1 subsite while providing calibrated probabilities and applicability-domain boundaries, thereby ensuring predictive reliability and avoiding overinterpretation. This methodological refinement mirrors recent QSAR guidance emphasizing rigorous validation and domain awareness for carbohydrase targets. In sum, while earlier research demonstrated that *M. indica* polyphenols can inhibit α-glucosidase and α-amylase, the current pipeline adds discrimination by clarifying which scaffolds remain credible once modern validation and AD criteria are applied, thus bridging traditional enzymology with robust predictive modeling to strengthen translational prospects. Your DPP-4 analysis also maps onto, but refines, the literature. A comprehensive review of natural DPP-4 inhibitors records *M. indica* leaf extract with in-vitro DPP-4 inhibition (IC_{50} ~ 182.7 µg/mL) and points to mangiferin as a principal active constituent (Suman & et al., 2016). Independent in-vivo work then shows mangiferin lowering serum DPP-4 and improving glycemic/insulin indices in high-fat/streptozotocin rat models, suggesting that its incretin-axis benefits are not merely *in silico* artifacts. Yet earlier reports often stopped at these observations; they did not systematically integrate physicochemical constraints, off-target ADMET flags, or generalize SAR beyond narrow series. Your consolidation closes that gap: you confirm that ~24–27% of *M. indica*–linked candidates exhibit consistent DPP-4–relevant features across studies, but only ~12–15% retain acceptable drug-likeness when Lipinski, Veber, and early clearance heuristics are enforced simultaneously. This is congruent with the enzymology DPP-4's S1/S2 pockets favor specific H-bonding and hydrophobic anchors but exposes why many phenolic glycosides underperform pharmacokinetically. Earlier reviews called for more rigorous triaging and standardized reporting; your approach operationalizes that ask with AD-bounded ML and a tri-pillar confirmation rule (QSAR/ML + docking + at least one *in vitro*/in-vivo datapoint), thereby upgrading DPP-4 natural-product claims from "interesting" to "screenable."

For PTP1B, your findings dovetail with two decades of work positioning flavonoids and xanthone glycosides like mangiferin as credible starting points. Early medicinal chemistry established that mangiferin derivatives could inhibit PTP1B and that judicious decoration improved activity over the parent (Hu & et al., 2007). Broader reviews later cataloged flavonoids as a prolific source of PTP1B binders, aided by computer-aided design (Almasri et al., 2021). What your review adds is clarity about series portability and model reliability: you show that while local SAR within single flavonoid series is robust (e.g., specific C-glycosylation patterns and ring substitutions), cross-series prediction degrades fast unless models are built on structurally diverse training sets and constrained by well-defined AD. This matches the modern view that PTP1B QSAR must temper attractive R^2/Q^2 with chemical-space diagnostics and independent tests before prioritizing syntheses. Moreover, your pipeline's insistence on *orthogonal* confirmation (e.g., calorimetry or targeted *in vitro* phosphatase assays wherever available) mitigates the known risks of overinterpreting docking poses at allosteric PTP1B surfaces. In short, where earlier studies proved *can inhibit*, your synthesis indicates *how to progress*: identify substituent vectors that trade polar surface for permeability without losing the H-bonding network essential for activity, and validate leads in AD-aware models to avoid series-specific optimism. That reframing is crucial if PTP1B is to move from appealing biology to tractable chemistry in the *M. indica* context.

Methodologically, the emphasis on external validation and applicability domain (AD) situates the work firmly within OECD-aligned QSAR practice and directly addresses discrepancies that have troubled earlier carbohydrase models. A growing body of critique highlights that many "high-performing" QSARs are trained only on narrow, congeneric series with internal cross-validation, which inflates generalizability and masks true predictive limits. By contrast, the present results where external-test AUC and MAE proved ~10–20% less optimistic than cross-validation mirror those warnings and underscore why AD reporting must accompany performance metrics. Methodological treatments now stress that QSAR reliability is conditional on domain membership and that predictions degrade sharply outside it, with best practice favoring structural and response-space diagnostics over single-distance heuristics (Gadaleta et al., 2016). This study reflects that guidance: by explicitly mapping the chemical manifold of the training set and flagging out-of-domain *M. indica* derivatives before they are advanced, the workflow reduces false positives and ensures that computational triage remains aligned with experimental feasibility. Such domain-aware screening explains why the fraction of "survivor" candidates here is smaller than in earlier narrative reviews yet more credible for follow-up at the bench. Moreover, the pipeline illustrates how transparency in AD handling not only

constrains overinterpretation but also raises the reproducibility bar for phytochemical QSAR, where scaffold diversity and heterogeneous bioassays often complicate inference. Going forward, convergence on community standards such as adopting shared train–test splits and publishing AD visualizations would enable apples-to-apples benchmarking across research groups and further close the optimism gap that has plagued carbohydrase modeling. In this sense, the contribution is methodological as well as chemical: it demonstrates that polyphenol-rich natural products can be filtered through validation- and domain-aware QSAR to yield a narrower, but more reliable, set of leads. By aligning predictive analytics with OECD best practice and current methodological consensus, the work exemplifies how phytochemical QSAR can evolve from overpromising screens toward actionable guidance for drug discovery.

Translationally, the discussion highlights a challenge often bracketed in earlier efficacy-focused reports: bioavailability. While mangiferin and its analogues display compelling enzymology sometimes achieving a-glucosidase potencies that rival or exceed reference drugs their oral bioavailability remains consistently poor, typically ≈1–2%, with low permeability and solubility constraining systemic exposure, as summarized in recent pharmacokinetic reviews). Contemporary analyses now emphasize that genuine therapeutic promise depends not only on potency but also on strategies to overcome these pharmacokinetic bottlenecks. Accordingly, two complementary tracks are widely recommended: chemistry-led interventions, such as prodrug approaches, partial de-glycosylation, isosteric substitutions, or ion-pairing, and formulation-led solutions, including nanocarriers, cyclodextrin inclusion complexes, and advanced polymer matrices (Shaikh et al., 2021). Each pathway seeks to enhance exposure while preserving the hydrogen-bonding motifs and aromatic contacts that underlie target engagement. In this context, the AD-aware prioritization presented here aligns well with translational needs: by identifying compound subseries that balance permeability and potency before formulation rescue becomes necessary, the workflow provides medicinal chemists with a shorter and more reliable route to in vivo confirmation. Conversely, for scaffolds that remain highly polar and resist medicinal-chemistry optimization, the findings support an exposure-first formulation plan deploying enabling technologies to establish proof-of-mechanism (e.g., post-prandial glucose lowering or DPP-4 modulation) directly in vivo. This dual emphasis recognizes that some leads may progress through molecular modification, while others are more feasibly advanced through formulation innovation, depending on their physicochemical liabilities. Importantly, this framing makes explicit what many earlier phytochemical studies only implied: that translation from enzymatic potency to therapeutic relevance requires parallel attention to absorption, distribution, and developability. By combining rigorous QSAR and AD-aware filtering with pharmacokinetic realities, the work bridges classic phytochemistry and modern drug-development thinking, offering a more actionable blueprint for moving *M. indica* polyphenols from in vitro promise toward clinical feasibility.

Finally, limitations and avenues for future work are evident from the comparative overview. The study inherits the assay heterogeneity that characterizes the field differences in substrates, enzyme sources, and readouts and although pIC_{50} harmonization reduces inter-study noise, true equivalence across experiments remains imperfect, a challenge repeatedly highlighted in QSAR and carbohydrase modeling literature (Singh et al., 2021). A key solution lies in community-wide adoption of shared, stratified train/validation/test splits for a-glucosidase, a-amylase, DPP-4, and PTP1B, coupled with preregistered AD reporting and minimal metadata including assay conditions and protein constructs to contextualize predictions. The results also illustrate how docking-only claims often fail under AD and external-test scrutiny, underscoring the need for a tri-pillar standard in future studies: calibrated ML models with AD, structure-based modeling, and at least one supporting experimental datapoint, alongside prospective validation on small, chemically diverse sets. Target-wise, dual inhibition of carbohydrases remains a compelling strategy, but programs targeting PTP1B and DPP-4 should prioritize permeability and clearance early, given the strong influence of polar surface area on bioavailability. In sum, this work reframes *M. indica*–derived antidiabetic discovery, moving from a literature of enticing but disparate signals toward a pipeline of tractable leads, provided the field integrates rigorous validation, domain-aware QSAR, and pharmacokinetically informed design. By explicitly linking potency, permeability, and AD-aware prediction, the study charts a roadmap for translating in vitro enzymology into actionable, in vivo-ready candidates, bridging classic phytochemistry with modern drug-discovery practice and offering a more reliable foundation for follow-up medicinal chemistry and preclinical testing.

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CONCLUSION

In conclusion, this systematic review of 113 peer-reviewed studies delivers a disciplined, decision-oriented picture of Mangifera indica–derived chemotypes for antidiabetic discovery and clarifies how to progress from promising signals to tractable leads. By harmonizing quantitative endpoints to pIC50/pKi, enforcing external testing with scaffold-aware splits, and applying an explicit applicability domain, the synthesis replaces optimism with calibrated, generalizable evidence. The results converge on a practical hierarchy of targets: intestinal a-glucosidase offers the most immediate path for translation, a-amylase provides complementary post-prandial control, and DPP-4 and PTP1B form a signaling tier that is attractive but requires early attention to selectivity, permeability, and exposure. Chemically, the weight of evidence points to polyphenolic families xanthones such as mangiferin, flavonols, and gallotannins as reproducible sources of activity, while also highlighting why many members of these series falter in vivo: polarity, glycosylation, and planarity can deliver strong enzyme recognition yet penalize absorption and distribution. The review's percentage-based audit underscores methodological strength: 100% external evaluation for headline metrics, 100% quantitative endpoint harmonization, and a strict subset in which 100% of analyses report applicability domain membership, scaffold or temporal splits, and leakage protections; together, these guardrails convert diffuse claims into a credible signal that roughly two fifths of "promising" hits survive scrutiny and a third remain drug-likeness plausible without heroic formulation. Three practical implications follow. First, prioritize a-glucosidase programs on xanthone and galloyl cores that already balance potency with manageable polarity; for such series, modest medicinal-chemistry edits or permeability-oriented prodrugs can deliver oral exposure. Second, treat DPP-4 and PTP1B scaffolds as optimization platforms rather than near-term candidates, building permeability and selectivity strategies into the design brief from the outset and rejecting models that perform well inside narrow, congeneric neighborhoods. Third, institutionalize triangulation: allow QSAR or docking to nominate, but require at least one orthogonal experiment and uncertainty reporting before elevating any structure to a lead. Equally important are the field-level recommendations that emerge from the comparison with prior literature. Shared, openly versioned datasets with predefined scaffold-novel train/validation/test splits would enable apples-to-apples benchmarking and shrink the optimism gap that has historically separated cross-validation from external performance. Minimal assay metadata standards enzyme source, substrate, buffer, and aggregation controls would further stabilize structure–activity narratives and reduce irreproducible outliers. Finally, the translational conversation must sit alongside enzymology from the start: where polarity cannot be engineered down without deleting recognition chemistry, rational formulation is not a last resort but a hypothesis-testing tool that can quickly confirm mechanism in vivo. Taken together, the evidence supports a confident but careful claim: Mangifera indica provides a mechanistically coherent and computationally navigable reservoir of antidiabetic chemotypes, and when models are validated externally, bounded by applicability domain, and paired with orthogonal data, they deliver predictions that are not only statistically sound but genuinely operationally useful for synthesis and screening. The path forward is clear focus the chemistry on tractable scaffolds, enforce transparent evaluation with uncertainty, integrate exposure thinking early, and publish reusable datasets and splits so that the next generation of studies moves from attractive in-silico figures to reproducible, bioavailable leads for real-world glycemic control.

RECOMMENDATIONS

To translate these findings into action, we recommend a single, coherent program built on rigorous data curation, leakage-proof modeling, orthogonal validation, and early developability planning: consolidate and openly release a harmonized, versioned dataset of *Mangifera indica* chemotypes with standardized quantitative endpoints (pIC_{50}/pK_i), full assay metadata (enzyme source, substrate, buffer, detection method, aggregation controls), and de-duplicated, normalized structures, and pair this with public, scaffold-aware train/validation/test splits so future models are directly comparable; preregister modeling protocols that fix a metric hierarchy (MAE/RMSE primary, R^2_ext/AUC secondary), enforce nested hyperparameter tuning, reserve an untouched external test for headline claims, and report uncertainty (prediction intervals) alongside point estimates; institutionalize an applicability-domain (AD) standard in which every prediction carries an AD flag from explicit structural/density diagnostics, performance is stratified in- vs. out-of-domain, and any out-of-domain "hit" is treated as hypothesis-generating only; adopt dual representation feature sets that combine compact physicochemical/topological descriptors with circular fingerprints, always publish a

transparent penalized-linear baseline, and compare advanced learners under identical splits and tuning budgets, favoring the simplest model that survives external and AD checks; require triangulation before elevation QSAR/ML bounded by AD plus reproducible structure-based analysis (documented protein state, pose stability, redocking controls) plus at least one orthogonal experimental datapoint (clean dose–response *in vitro* or minimal *in vivo* signal) and document precisely which pillars each candidate satisfies; design with developability from day one by prioritizing, for α-glucosidase/α-amylase, xanthone and galloyl cores that balance potency and polarity, and by building permeability/selectivity strategies early for DPP-4 and PTP1B (prodrugs, isosteres, judicious ring substitutions, ion-pairing), while planning exposure-first, formulation-enabled tests when polarity cannot be engineered down without erasing recognition chemistry; standardize assay practices via a concise reporting checklist, convert all activities to molar units and pIC_{50}/pK_i, capture confidence intervals and potential confounders to support weighted meta-analysis, and report decision-relevant errors and calibration (MAE/RMSE with 95% prediction intervals, calibration plots, residuals) rather than relying on correlations or docking scores alone; run prospective, diversity-first validation on a small panel spanning AD space, publish negative as well as positive results to refine boundaries and avoid repeated exploration of dead-end motifs; ensure full reproducibility by releasing code, containers, dependency locks, and "run-once" scripts, plus model cards detailing data, splits, features, hyperparameters, AD method, and known failure modes; support quality at scale with author and reviewer checklists that gate leakage, AD reporting, external tests, assay metadata, and uncertainty; execute a pragmatic 90–180-day roadmap 0–30 days to finalize the curation schema, freeze v1.0 data and public splits, and publish the protocol; 30–90 days to train baselines and advanced models under nested tuning, produce AD and calibration artifacts, and preregister the prospective panel; 90–180 days to run the diversity-first experiment, integrate outcomes, release v1.1 with new labels, update models and documentation, and publish a brief emphasizing external generalization; extend beyond the four primary targets only after stable prospective predictivity is demonstrated, adding mechanisms one at a time under the same external/AD discipline; incorporate bibliometrics cautiously as context rather than quality proxies and finally, prioritize equity and safety by assessing sustainable sourcing, potential herb–drug interactions, and excluding scaffolds with structural alerts or PAINS behavior. Taken together, these integrated recommendations convert an attractive literature into an executable pipeline that consistently yields externally validated, AD-bounded, and bioavailability-conscious leads ready for medicinal chemistry and translational testing.

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