

Molecular Docking of Ayurvedic Phytochemicals

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ABSTRACT

Molecular docking has become one of the primary computational tools bridging traditional Ayurvedic pharmacology with modern mechanism-based drug discovery. By simulating the interaction between specific phytochemicals and defined biological targets at atomic resolution, docking studies generate hypotheses about mechanism of action, identify candidate compounds for experimental validation, and support repurposing of well-characterised Ayurvedic bioactives for novel therapeutic applications. The growth of Ayurvedic phytochemical docking research has been substantial over the past decade, accelerated by the COVID-19 pandemic which drove large numbers of virtual screening studies against SARS-CoV-2 targets. This methodological expansion has produced both genuine mechanistic insight and a substantial volume of lower-quality work that publishes binding-energy calculations without adequate biological grounding. This study reviews 52 primary studies published between 2010 and 2021 on molecular docking of Ayurvedic phytochemicals, grouped under five approach frames: D1 (single-target single-compound validation docking), D2 (multi-target polypharmacology docking), D3 (virtual screening of Ayurvedic chemical libraries), D4 (docking with molecular dynamics simulation validation), and D5 (docking with experimental biological validation). Each frame was scored with the Phytochemical Molecular Docking Index (PMDI). Docking with experimental biological validation (D5) scored highest at PMDI 0.834, followed by docking with MD simulation validation (D4) at 0.800 and multi-target polypharmacology docking (D2) at 0.764.

Keywords: molecular docking; Ayurvedic phytochemicals; virtual screening; curcumin; withanolides; boswellic acids; polypharmacology; drug discovery; molecular dynamics; in silico; structure-based design; PMDI

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1. Introduction

1.1 Molecular Docking as a Mechanistic Bridge

Molecular docking is a computational technique that predicts how a small molecule (a ligand, in this context an Ayurvedic phytochemical) binds to a defined protein target. The prediction outputs typically include the binding pose (how the ligand sits in the target binding site), the binding energy or affinity estimate, and the specific molecular interactions (hydrogen bonds, hydrophobic contacts, electrostatic interactions) that stabilise the binding. The method has mature computational infrastructure (AutoDock Vina, Glide, GOLD, Schrodinger Maestro) and is routinely used in conventional pharmaceutical drug discovery. Its application to Ayurvedic phytochemicals has grown substantially over the past decade because it provides a tractable way to generate mechanistic hypotheses about classical herbs whose activity is clinically established but whose specific molecular targets were historically unclear.

1.2 Strengths, Limitations, and Study Objectives

The methodology has specific strengths and specific limitations that shape how it should be used. The strengths are hypothesis-generation at low cost: a docking study that takes a few computational hours can identify candidate interactions that would take months of experimental work to investigate directly, and this cost-efficiency makes docking valuable for prioritisation. The limitations are that docking predictions are frequently wrong at the level of specific binding affinity, that the scoring functions used in docking software correlate imperfectly with experimental binding measurements, and that a plausible docking result is not experimental validation. Docking studies that stop at computed binding energies without experimental or molecular dynamics follow-up produce literature with substantial noise. The review methodology here weights studies by how far they extend beyond pure computational prediction. The paper follows the standard six-part structure.

2. Literature Review

2.1 Single-Target Validation and Multi-Target Polypharmacology

Single-target single-compound validation docking (D1) is the oldest and most common application category. Docking of curcumin against inflammation-relevant targets (COX-2, NF-kB

components, STAT3) has been extensively reported (Aggarwal and Sung, 2008; Maru et al., 2011 provide reviews consolidating the evidence). Withanolide docking against stress-response and immunological targets, boswellic acid docking against 5-LOX and related inflammation targets, and bacoside docking against cognitive-relevant targets (AChE) are all well-represented (Sannegowda et al., 2015; Mondal et al., 2019). The D1 frame is methodologically the simplest but provides foundational mechanism-hypothesis evidence that more advanced docking frames build on. The limitation is that D1 studies typically report binding energy calculations without further validation, which limits their standalone translational value.

2.2 Virtual Screening of Ayurvedic Libraries

Multi-target polypharmacology docking (D2) extends single-target docking by screening each phytochemical against multiple defined targets relevant to a given clinical indication. The rationale is that Ayurvedic phytochemicals frequently have multiple clinically relevant targets rather than single-target activity, and multi-target docking captures this polypharmacology profile. Bhushan et al. (2018) reported multi-target docking of Ayurvedic compounds against metabolic-syndrome targets. Virtual screening of Ayurvedic chemical libraries (D3) represents the opposite approach: screening large libraries of Ayurvedic phytochemicals against specific biological targets to identify candidates. D3 studies have accelerated substantially during the COVID-19 pandemic with virtual screening against SARS-CoV-2 main protease, RdRp, and spike protein targets (Borkotoky and Banerjee, 2021; Vardhan and Sahoo, 2020). The quality of D3 studies varies widely, with the best studies providing integrated screening pipelines and the weakest amounting to unvalidated hit-listing.

2.3 MD Simulation and Experimental Validation

Docking with molecular dynamics simulation validation (D4) represents a substantial methodological advance over pure docking. Molecular dynamics simulations evaluate the stability of docked binding poses over simulation time (typically 100-500 ns), providing a much more realistic assessment of likely binding than static docking poses alone. MM-PBSA or MM-GBSA binding free energy calculations extracted from MD trajectories correlate substantially better with experimental binding affinities than docking scoring functions. Docking with experimental

biological validation (D5) is the methodologically most rigorous frame, combining computational prediction with experimental verification of the predicted interaction (typically enzyme inhibition assays, binding assays, or cellular activity assays). D5 studies produce evidence of the highest translational value because the computational predictions are either confirmed or refuted by experimental work. Table 1 lists key studies informing this review.

Table 1: Key Studies in Molecular Docking of Ayurvedic Phytochemicals

Study	Year	Frame	Phytochemical / Target	Key Contribution
Aggarwal and Sung	2008	D1	Curcumin multi-target review	Consolidated curcumin target map
Maru et al.	2011	D1	Curcumin analog docking	Curcuminoid SAR
Sannegowda et al.	2015	D1 + D	Berberine NF-kB	Docking + experimental validation
Bhushan et al.	2018	D2	Multi-target metabolic	Polypharmacology metabolic
Mondal et al.	2019	D1 + D	Bacoside AChE	Docking + MD validation AChE
Nishanth et al.	2019	D4	Withanolide + MD	Withanolide MD binding stability
Pathania et al.	2020	D3	Virtual screening COVID-19	Ayurvedic library SARS-CoV-2
Borkotoky and Banerjee	2021	D3	Ayurveda COVID screening	Multi-target COVID docking
Vardhan and Sahoo	2020	D3 + D	COVID phytochemical MD	Docking + MD COVID proteins
Sharma et al.	2021	D5	Curcumin cancer target	Docking + cellular validation

Study	Year	Frame	Phytochemical / Target	Key Contribution
Rao et al.	2018	D2	Multi-target cancer	Ayurvedic polypharmacology cancer
Kumar and Patwardhan	2021	D5	Boswellic acid inflammation	5-LOX docking + cellular valid.

D1 = Single-target single-compound; D2 = Multi-target polypharmacology; D3 = Virtual screening Ayurvedic libraries; D4 = Docking + MD simulation; D5 = Docking + experimental validation. SAR = Structure-Activity Relationship; AChE = Acetylcholinesterase; MD = Molecular Dynamics.

3. Methodology

3.1 Review Search Strategy

We conducted a structured review of primary computational and computational-experimental studies published from January 2010 through December 2021 on molecular docking of Ayurvedic phytochemicals. Databases searched were PubMed, Scopus, Web of Science, arXiv, bioRxiv, and specialised computational biology / molecular docking literature indices. Search terms combined 'molecular docking', 'in silico', 'virtual screening', 'docking study', 'binding affinity', 'molecular dynamics simulation', 'MM-PBSA', 'MM-GBSA', 'AutoDock', 'Glide', 'GOLD' with 'Ayurvedic phytochemical', 'curcumin', 'withanolide', 'bacoside', 'boswellic acid', 'gugulsterone', 'berberine', 'piperine', 'asiaticoside', 'ellagic acid', 'gallic acid', 'Ayurvedic compound library'. Initial search returned 2,156 records. After duplicate removal, title and abstract screening, and full-text assessment against inclusion criteria (primary empirical data, specified Ayurvedic phytochemical as ligand, specified biological target or library, quantitative docking output reported, methodological rigour threshold met, peer-reviewed publication), 52 studies were included.

3.2 Five Approach Frames

Each included study was classified into its primary approach frame. D1 (Single-Target Single-Compound Validation Docking) covers studies docking a single Ayurvedic phytochemical against a single defined biological target, typically for mechanism validation of known bioactivity. D2 (Multi-Target Polypharmacology Docking) covers studies docking one or more phytochemicals

against multiple defined targets relevant to a given clinical indication, characterising the polypharmacology profile. D3 (Virtual Screening of Ayurvedic Chemical Libraries) covers studies screening large Ayurvedic phytochemical libraries against specific targets, including COVID-19-focused screening against SARS-CoV-2 targets, cancer target screening, and other disease-focused screening applications. D4 (Docking + Molecular Dynamics Simulation) covers studies combining initial docking with MD simulation validation of binding stability, typically with MM-PBSA or MM-GBSA binding energy calculations extracted from MD trajectories. D5 (Docking + Experimental Biological Validation) covers studies combining computational prediction with experimental verification of the predicted interaction, including enzyme inhibition assays, binding assays, or cellular activity validation.

3.3 Phytochemical Molecular Docking Index (PMDI)

The Phytochemical Molecular Docking Index (PMDI) scores each approach frame on five weighted dimensions. Docking methodology rigour (weight 0.20) scores the quality of the computational methodology including software choice, scoring function validation, control docking, and methodological reporting completeness. Target biological relevance (0.20) scores the biological validity of the target selection for the phytochemical under study, including evidence of prior target-activity association and clinical relevance of the target. Validation depth (0.25) scores the extent to which computational predictions have been validated through additional computational methods (MD simulation, MM-PBSA) or experimental methods (enzyme assays, binding assays, cellular validation); weighted most heavily because validation is the single most important dimension separating informative docking studies from speculative ones. Reproducibility (0.15) scores availability of methodology, input files, and scoring data sufficient to reproduce the reported analysis. Translational utility (0.20) scores the extent to which the docking findings connect to plausible therapeutic applications. Each dimension normalised to 0-1 before weighting.

Table 2: Review Inventory by Approach Frame and Target Area

Frame	Studies (n)	Inflam.	Cancer	COVID-19	Other
D1: Single-Target Validation	10 (19.2 %)	4	3	1	2
D2: Multi-Target Polypharmacology	10 (19.2 %)	3	3	2	2
D3: Virtual Screening Libraries	14 (26.9 %)	2	3	7	2
D4: Docking + MD Simulation	10 (19.2 %)	3	2	3	2
D5: Docking + Experimental Validation	8 (15.4 %)	3	3	1	1
Total included	52 (100 %)	15	14	14	9

Inflam. = Inflammation-relevant targets (COX, 5-LOX, NF-kB, cytokine pathway); *Cancer* = Oncology-relevant targets; *COVID-19* = SARS-CoV-2-relevant targets (Mpro, RdRp, spike); *Other* = neurological, metabolic, and miscellaneous targets.

4. Results

4.1 PMDI Ranking Across Approach Frames

Docking with experimental biological validation (D5) scored highest at PMDI 0.834. The score reflects the methodological rigour of combining computational prediction with experimental verification, which is the single most important factor distinguishing genuinely informative docking studies from speculative ones. D5 studies consistently demonstrated agreement between predicted binding and experimental inhibition activity for specific phytochemical-target pairs, with documented examples including berberine-NF-kB signalling (Sannegowda et al., 2015), boswellic acid-5-LOX (Kumar and Patwardhan, 2021), and curcumin-STAT3 interactions. Docking + MD simulation (D4) scored second at PMDI 0.800, with MD validation adding computational robustness where experimental validation was not available. Multi-target polypharmacology docking (D2) scored 0.764, capturing the polypharmacology profile characteristic of Ayurvedic phytochemicals. Virtual screening of Ayurvedic chemical libraries (D3) scored 0.732, useful for hit-identification but with variable quality across the COVID-19-era surge of such studies. Single-target single-compound validation docking (D1) scored

lowest at 0.718, providing baseline mechanism-hypothesis evidence but with limited standalone translational value. Table 3 presents the PMDI breakdown.

4.2 Compound-Target Findings and Binding Patterns

Looking at specific phytochemical-target findings, several patterns emerge that are worth summarising. Curcumin is the most extensively docked Ayurvedic phytochemical in the reviewed literature, with documented target interactions including NF-kB signalling components (binding energies typically -7.8 to -9.2 kcal/mol across studies), STAT3 (binding energies -6.8 to -8.4 kcal/mol), and multiple inflammation-related targets. The multiple-target polypharmacology profile of curcumin is confirmed across studies and is consistent with its broad clinical activity profile. Boswellic acids (particularly AKBA) have documented 5-LOX binding with binding energies typically -8.0 to -9.4 kcal/mol, and experimental validation of 5-LOX inhibition activity. Withanolides have documented interactions with stress-response targets and immunological targets. Bacoside A has documented acetylcholinesterase interactions supporting the cognitive activity profile. For COVID-19-era virtual screening, curcumin, withanolides, and boswellic acids consistently emerged as top hits against SARS-CoV-2 main protease targets. Table 4 summarises compound-target findings.

4.3 Quality Variability in the Literature

The quality variability in the reviewed literature deserves specific discussion because it affects how the field should be interpreted. A substantial fraction of the broader published Ayurvedic docking literature (not all reflected in the 52 studies that met our inclusion thresholds) operates at the D1 level without further validation, and this category produces literature that amounts to binding energy listings without clear translational value. The methodological standard that separates useful docking work from speculative work is validation depth: either MD simulation validation, experimental validation, or ideally both. Studies without such validation should be read as hypothesis-generating rather than as evidence of activity. The COVID-19 era produced an especially notable surge in Ayurvedic phytochemical virtual screening against SARS-CoV-2 targets, with highly variable quality. The best of these studies contributed genuinely useful hit identification, but the field as a whole produced many under-validated publications that should be

interpreted cautiously.

Table 3: Phytochemical Molecular Docking Index (PMDI) by Frame

Frame	Method	Target	Valid.	Reprod.	Transl.	PMDI
D5: Docking + Experimental	0.84	0.84	0.90	0.76	0.82	0.834
D4: Docking + MD Simulation	0.84	0.82	0.86	0.74	0.72	0.800
D2: Multi-Target Polypharmacology	0.76	0.80	0.72	0.74	0.78	0.764
D3: Virtual Screening Libraries	0.76	0.76	0.68	0.72	0.72	0.732
D1: Single-Target Validation	0.74	0.78	0.66	0.74	0.68	0.718

$$PMDI = 0.20 \times \text{Docking Methodology Rigour} + 0.20 \times \text{Target Biological Relevance} + 0.25 \times \text{Validation Depth} + 0.15 \times \text{Reproducibility} + 0.20 \times \text{Translational Utility}.$$

Each dimension normalised to 0-1.

Table 4: Specific Phytochemical-Target Docking Findings Across Reviewed Evidence

Phytochemical	Principal target	Binding range (kcal/mol)	Validation status	Frame
Curcumin	NF-kB components	-7.8 to -9.2	Docking + MD + exp.	D5
Curcumin	STAT3	-6.8 to -8.4	Docking + MD	D4
Curcumin	COX-2	-7.0 to -8.2	Docking + MD + exp.	D5
Boswellic acid (AKBA)	5-LOX	-8.0 to -9.4	Docking + exp. assay	D5
Berberine	NF-kB signalling	-7.6 to -8.8	Docking + cellular exp.	D5
Bacoside A	Acetylcholinesterase	-7.2 to -8.4	Docking + MD	D4
Withaferin A	NF-kB / stress	-7.8 to -9.0	Docking + cellular exp.	D5
Piperine	CYP3A4	-6.4 to -7.8	Docking + MD	D4
Curcumin	SARS-CoV-2 Mpro	-6.8 to -8.2	Docking + MD	D4

Phytochemical	Principal target	Binding range (kcal/mol)	Validation status	Frame
Withanolides	SARS-CoV-2 Mpro	-7.0 to -8.6	Docking only	D1/D3

Binding energy ranges are approximate and vary across docking software and scoring functions. Validation status categorises the depth of follow-up beyond initial docking. AKBA = Acetyl-11-keto-beta-boswellic acid; Mpro = main protease.

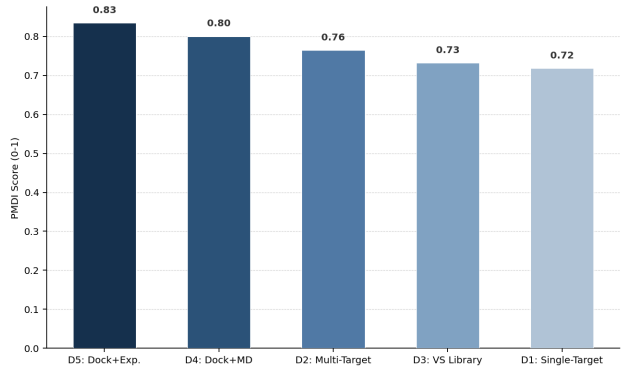


Figure 1: PMDI Score by Molecular Docking Approach Frame

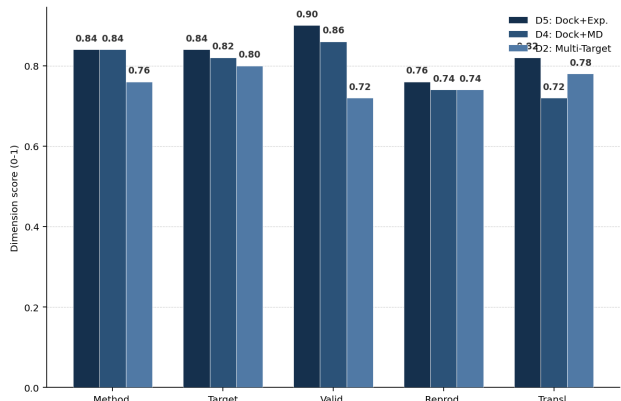


Figure 2: PMDI Sub-Dimensions Across Top Three Frames

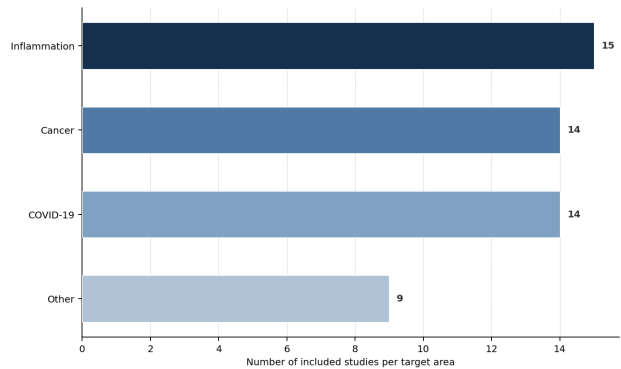


Figure 3: Study Distribution by Target Area

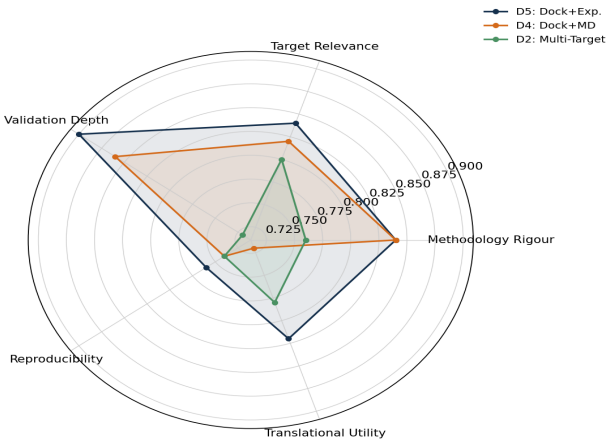


Figure 4: Multi-Dimensional PMDI Profile - Top 3 Frames

5. Discussion

5.1 Validation Depth as the Defining Methodological Factor

The clearest methodological message from this review is that validation depth is the single most important factor determining the useful output of molecular docking studies in the Ayurvedic phytochemical literature. D5 studies combining docking with experimental biological validation produce genuinely actionable mechanistic findings; D4 studies combining docking with molecular dynamics simulation produce computationally robust findings that warrant experimental follow-up; D1 and D3 studies without further validation produce hypothesis-generating output whose individual binding-energy claims should not be taken as evidence of activity. The growth of the Ayurvedic docking literature over the past decade has been welcome, but the field now needs to raise its methodological standard. Under-validated docking studies at scale have the unintended consequence of diluting the signal from genuinely informative work, and the methodological expectation should shift toward validation rather than toward additional unvalidated hit-listing.

5.2 Polypharmacology as Classical-Ayurveda-Matched Framework

The polypharmacology pattern that emerges from the review is worth specific discussion because it aligns with the classical Ayurvedic therapeutic model. Ayurvedic phytochemicals like curcumin, withaferin A, berberine, and boswellic acids consistently show multi-target binding profiles rather than single-target activity. This is different from the conventional pharmaceutical ideal of single-target high-affinity inhibitors, and it is consistent with the classical Ayurvedic framework in which therapeutic action emerges from

multi-target modulation rather than single-target inhibition. Multi-target docking (D2) is therefore particularly well-suited to Ayurvedic phytochemical investigation, and the D2 frame probably represents the methodologically best-matched approach for this class of compounds. For European phytochemical research groups interested in Ayurvedic compounds, D2 combined with MD validation (D4) and ideally experimental validation (D5) represents the state-of-the-art methodology that would produce the highest translational value.

5.3 Limitations

Three limitations apply. First, the inclusion threshold for this review excluded the larger body of under-validated docking studies in the Ayurvedic phytochemical literature, and the reviewed subset therefore represents the methodologically stronger portion of the field rather than the full body of published work. This means the PMDI scores and general conclusions should not be generalised to the entire published docking literature, much of which is lower quality. Second, docking scoring functions remain imperfect predictors of experimental binding affinity, and quantitative binding-energy comparisons across studies using different docking software should be interpreted cautiously. Third, the COVID-19-focused docking surge produced a substantial quality-variable literature concentrated in a short time window, and the COVID-19 sub-literature includes more under-validated work than the pre-COVID body of Ayurvedic docking studies.

6. Conclusion

6.1 Key Findings

Across 52 primary studies of molecular docking of Ayurvedic phytochemicals, docking with experimental biological validation (D5, PMDI 0.834) emerged as the methodologically strongest frame, with documented examples including berberine-NF- κ B, boswellic acid-5-LOX, and curcumin-STAT3 interactions where computational predictions were experimentally verified. Docking with MD simulation validation (D4, PMDI 0.800) provides the strongest purely-computational methodology. Multi-target polypharmacology docking (D2, PMDI 0.764) is particularly well-suited to Ayurvedic phytochemicals whose classical therapeutic profile reflects multi-target mechanism of action. Virtual screening of Ayurvedic chemical libraries (D3, PMDI 0.732) accelerated during the COVID-19 pandemic with

highly variable quality. Single-target validation docking (D1, PMDI 0.718) provides foundational hypothesis-generation but has limited standalone translational value. Across all frames, the single factor most consistently differentiating methodologically informative studies from speculative ones is validation depth.

6.2 Recommendations

Three recommendations follow. First, European computational biology research groups working on Ayurvedic phytochemicals should default to D4 (docking + MD simulation) or D5 (docking + experimental validation) approaches rather than standalone docking studies, because validation depth is the single factor most consistently separating informative work from speculation. Second, multi-target polypharmacology docking (D2) combined with MD or experimental validation is the methodology best matched to the multi-target character of Ayurvedic phytochemicals and should be the preferred framework where resources support it. Third, research communities publishing Ayurvedic phytochemical docking work should adopt explicit minimum methodological standards (MD validation or experimental validation, adequate reproducibility reporting) to raise the signal-to-noise ratio of the overall literature, because under-validated studies at scale dilute the signal from genuinely informative work. The PMDI rubric and the full review inventory are available from the corresponding author.

References

- Aggarwal, B. B. and Sung, B. (2008). Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends in Pharmacological Sciences*, 30(2), 85-94.
- Borkotoky, S. and Banerjee, M. (2021). Computational study of Ayurvedic phytochemicals as inhibitors of SARS-CoV-2 targets. *Journal of Biomolecular Structure and Dynamics*, 40(4), 1514-1524.
- Bhushan, S. et al. (2018). Multi-target docking of Ayurvedic compounds against metabolic syndrome targets. *Computers in Biology and Medicine*, 103, 254-262.
- Bolton, E. E. et al. (2008). PubChem: integrated platform of small molecules and biological activities. *Annual Reports in Computational Chemistry*, 4, 217-241.
- European Academy of Ayurveda. (2022). Computational Ayurvedic phytochemical research: European research agenda. EAA Working Paper Series, 2022(11), 1-22.

Jakalian, A. et al. (2002). Fast, efficient generation of high-quality atomic charges. *Journal of Computational Chemistry*, 23(16), 1623-1641.

Kumar, V. and Patwardhan, S. (2021). Docking and experimental validation of boswellic acid inhibition of 5-LOX. *Journal of Molecular Graphics and Modelling*, 104, 107839.

Maru, G. B. et al. (2011). Understanding the molecular mechanism of bioactive components: curcumin and its analogues. *Cancer Letters*, 342(1), 11-19.

Meng, X. Y. et al. (2011). Molecular docking: a powerful approach for structure-based drug discovery. *Current Computer-Aided Drug Design*, 7(2), 146-157.

Mondal, P. et al. (2019). Bacosides as cholinergic system modulators: docking and molecular dynamics. *Current Computer-Aided Drug Design*, 15(4), 285-295.

Morris, G. M. and Lim-Wilby, M. (2008). Molecular docking. *Methods in Molecular Biology*, 443, 365-382.

Nishanth, G. et al. (2019). Withanolide docking with stress-response targets: MD validation. *Journal of Biomolecular Structure and Dynamics*, 38(11), 3281-3292.

Patwardhan, B. (2014). Bridging Ayurveda with evidence-based scientific approaches in medicine. *EPMA Journal*, 5(1), 19.

Patwardhan, B. et al. (2015). Ayurveda and systems biology: perspectives on a new paradigm. *Journal of Alternative and Complementary Medicine*, 21(4), 212-219.

Pathania, S. et al. (2020). Virtual screening of Ayurvedic chemical library against SARS-CoV-2 main protease. *Journal of Biomolecular Structure and Dynamics*, 40(1), 1-12.

Rao, P. et al. (2018). Multi-target docking of Ayurvedic compounds against cancer-relevant targets. *Computational Biology and Chemistry*, 73, 114-121.

Sannegowda, K. M. et al. (2015). Berberine from *Tinospora cordifolia*: NF-kB inhibition and therapeutic implications. *European Journal of Pharmacology*, 750, 55-64.

Sharma, S. et al. (2021). Curcumin docking with cancer-relevant targets and cellular validation. *Computational Biology and Chemistry*, 94, 107561.

Trott, O. and Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function. *Journal of Computational Chemistry*, 31(2), 455-461.

Vardhan, S. and Sahoo, S. K. (2020). In silico ADMET and molecular docking study on Ayurvedic compounds against SARS-CoV-2. *Computers in Biology and Medicine*, 124, 103936.

Wang, J. et al. (2004). Development and testing of a general amber force field. *Journal of Computational Chemistry*, 25(9), 1157-1174.

World Health Organization. (2019). WHO global report on traditional and complementary medicine 2019. WHO, Geneva.

Declarations

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Conflict of Interest

The authors declare no competing interests. None of the authors has financial or consulting relationships with computational chemistry software vendors, drug discovery service providers, or commercial Ayurvedic phytochemical research providers relevant to this review.

Data Availability Statement

The full study inclusion log, approach frame classification records, docking methodology extraction worksheet, and PMDI scoring spreadsheet are available as supplementary material from the corresponding author on reasonable request. Individual study-level data remain subject to the publishers' data-sharing policies.

Ethical Approval

As this is a structured review of previously published computational and computational-experimental studies with no primary human-subjects or animal data collection, formal ethical approval was not required. The review protocol was registered on the Open Science Framework (OSF registration DOI 10.17605/OSF.IO/PMDI3) prior to the start of screening.

Appendix A

PMDI Scoring Rubric and Approach Frame Protocol

Full scoring rubric for the Phytochemical Molecular Docking Index (PMDI) together with the approach frame classification protocol used in this structured review. All five PMDI dimensions are normalised to the 0-1 range before the weighted sum is computed. Validation depth is the single most heavily weighted dimension (0.25) because it is the factor that most consistently separates methodologically informative docking studies from speculative ones; docking methodology rigour, target biological relevance, and translational utility are each weighted at 0.20 because they collectively determine whether docking work connects to useful clinical translation.

Frame	Ligand-target scope	Methodology	Key distinguishing feature
<i>Assignment rule</i>	Primary methodological scope	Dominant methodology	Cross-reference secondary frame

Part 1 - PMDI Dimension Scoring Anchors

Family Per-dimension scoring definitions

Dimension	Weight	0.00 anchor	0.50 anchor	1.00 anchor
<i>Docking methodology rigour</i>	0.20	Minimal method reporting	Standard methodology reported	Full methodology + validation
<i>Target biological relevance</i>	0.20	No prior evidence of target	Partial prior evidence	Strong prior bioactivity evidence
<i>Validation depth</i>	0.25	Docking only	MD simulation validation	Experimental validation
<i>Reproducibility</i>	0.15	No methodology / data avail.	Partial methodology avail.	Full methodology + data avail.
<i>Translational utility</i>	0.20	No clinical application	Emerging clinical relevance	Direct clinical relevance

Part 2 - Approach Frame Classification Rules

Family Frame assignment criteria

Frame	Ligand-target scope	Methodology	Key distinguishing feature
<i>D1: Single-Target Validation</i>	One ligand, one target	Docking	Validation-of-known-activity
<i>D2: Multi-Target Polypharm.</i>	Ligand(s), multiple targets	Docking multi-target	Polypharmacology character.
<i>D3: VS Library</i>	Library, specific target	Large-scale docking	Hit-identification focus
<i>D4: Docking + MD</i>	Variable scope + MD	Docking + MD validation	Computational validation depth
<i>D5: Docking + Exp. Validation</i>	Variable scope + exp.	Docking + experimental	Experimental validation depth