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COMPUTATIONAL EVALUATION OF ASHWAGANDHA COMPOUNDS AGAINST ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease involves several processes, and compounds acting at more than one relevant target warrant investigation. The present study examines twelve constituents of *Withania somnifera* against acetylcholinesterase, butyrylcholinesterase, beta secretase 1, glycogen synthase kinase 3 beta and cyclooxygenase 2. The reported dissertation dataset was evaluated using molecular docking scores, pharmacokinetic predictions and target network information. Fifteen compounds, including three reference drugs, provided 75 docking combinations. Withaferin A and Ashwagandhanolide shared the lowest butyrylcholinesterase score of −11.725 kcal/mol. Withanolide D gave the lowest beta secretase 1 score of −10.670 kcal/mol. Sitoindoside IX ranked first among the phytochemicals against the remaining three targets. Six aglycones were reported with zero Lipinski violations, whereas none of the phytochemicals had a favourable reported brain penetration prediction. Withaferin A, Withanolide D, Sitoindoside IX and Ashwagandhanolide warrant further evaluation, with Withanolide A retained as a comparator. The findings provide a preliminary basis for compound selection. Unresolved input and validation records limit reproducibility, and experimental studies are required to establish inhibition, exposure and biological activity.

KEYWORDS: *Withania somnifera*; Alzheimer's disease; molecular docking; butyrylcholinesterase; withanolides; pharmacokinetics.

INTRODUCTION

Alzheimer's disease involves several biological processes. Amyloid production, altered cholinergic transmission, tau phosphorylation and inflammatory signalling offer different points of investigation. BACE1 initiates the amyloidogenic cleavage of amyloid precursor protein.[1] Histochemical studies detected butyrylcholinesterase activity in hippocampal and temporal neocortical regions receiving cholinergic input.[2] GSK3 inhibition reduced tau phosphorylation in cells.[3], while structural studies of COX2 defined its interactions with fenamic acid inhibitors.[4] These findings support investigation of a target panel; they do not establish that inhibiting every target will be beneficial.

Ashwagandha contains chemically distinct constituents. Kuboyama and colleagues observed neuritic regeneration and synaptic reconstruction with Withanolide A in experimental systems.[5] Sehgal and colleagues reported effects of a Withania extract on amyloid pathology in mice, with a role for hepatic clearance.[6] Choudhary and colleagues isolated withanolides with cholinesterase inhibitory activity.[7] These observations provide a basis for examining individual compounds. They cannot be assigned indiscriminately to every constituent of the plant.

MATERIALS AND METHODS

Study material and scope

The study comprised molecular docking, pharmacokinetic assessment, target prediction and network analysis. The numerical dataset was obtained from the 2026 dissertation Computational Evaluation of Ashwagandha Compounds against Alzheimer's Disease.[8] This manuscript presents those reported results with verified structural metadata and a revised interpretation. The complete docking table was used for numerical comparisons. No additional docking simulations were performed during manuscript preparation..

Protein structures

Five human proteins were examined: acetylcholinesterase (AChE), butyrylcholinesterase (BChE), beta secretase 1 (BACE1), glycogen synthase kinase 3 beta (GSK3β) and cyclooxygenase 2 (COX2). The crystal structures are listed in Table 1. The deposited inhibitors are donepezil in 4EY7.[9], tacrine in 4BDS[10], compound 28 in 6EJ2[11], AR A014418 in 1Q5K[3] and meclofenamic acid in 5IKQ.[4] The original preparation files are required to resolve discrepancies between these deposited ligands and the redocking description in the dissertation.[8]

Table 1: Protein Structures and Verified Crystallographic Metadata.

Target	PDB	Resolution, Å	Deposited inhibitor
AChE	4EY7	2.35	Donepezil
BChE	4BDS	2.10	Tacrine
BACE1	6EJ2	1.46	Compound 28
GSK3β	1Q5K	1.94	AR A014418
COX2	5IKQ	2.41	Meclofenamic acid

PDB identifiers link to the deposited records. Metadata verified on 5 September 2026.

Ligand selection and preparation

Twelve phytochemicals and three comparators were included, as listed in Table 2. The dissertation reports retrieval from PubChem[8,12], conversion of unavailable three dimensional structures using Open Babel, and energy minimisation with MMFF94.[8,13] Hydrogen addition, Gasteiger charge assignment and conversion to PDBQT are reported.[8] Receptor preparation involved removal of water and selected heteroatoms, hydrogen addition and PDBQT conversion. The exact protonation assignment, retained cofactors, receptor chains and prepared structures were not supplied. These details are necessary for reproduction, including assessment of BACE1 protonation and COX2 cofactor handling.

Docking protocol and validation

The dissertation reports AutoDock Vina version 1.2.5, exhaustiveness of 8 and nine requested modes for each ligand and receptor combination.[8] The Vina method and subsequent software developments are described elsewhere.[14,15] The search region was described as centred on the deposited ligand, but numerical grid centres and dimensions were not provided. The lowest reported score was selected for each combination. The matrix contains 75 ligand and target combinations. These are not independent replicates; likewise, nine requested modes do not constitute nine independent experiments.

The dissertation states that redocking deviations were below 2.0 Å for all five receptors.[8] However, individual values, atom mappings, structural alignments and redocked coordinates were not supplied. Accordingly, this manuscript records validation as reported but not independently confirmed. The discrepancy in deposited ligand identities is relevant to that qualification. A favourable score for a reference compound cannot replace a documented pose recovery test.

Pharmacokinetic and target predictions

The dissertation assigns fourteen compounds to SwissADME and Ashwagandhanolide to pkCSM.[8] These platforms provide pharmacokinetic and physicochemical predictions.[16,17] Reported descriptors included molecular weight, lipophilicity, hydrogen bond counts, gastrointestinal absorption and brain penetration. Lipinski rules were used to assess physicochemical suitability.[18] SwissADME brain classifications and pkCSM logBB estimates were interpreted separately because they are different model outputs.[16,17,19] Original input strings and server exports were unavailable for independent reconstruction.

The source reports SwissTargetPrediction for Withaferin A, Withanolide D, Withanoside IV and Sitoindoside IX, and SuperPred for Ashwagandhanolide.[8] Method publications describe the respective prediction platforms.[20,21] Human target predictions were interpreted as hypotheses of possible molecular association. Their probability outputs were not pooled across platforms. Specific server versions and complete input strings were unavailable, so these publications do not establish which server revision produced the dissertation results.

Network analysis and numerical interpretation

The source reports STRING version 11.5, an interaction score threshold of 0.700 and Homo sapiens as the organism, followed by visualisation in Cytoscape version 3.9.[8] STRING records protein associations, and Cytoscape supports network analysis and visualization.[22,23] The edge list, exact degree values and enrichment statistics were not supplied, so network findings were considered qualitative. No significance tests, confidence intervals or binding constants were derived from docking scores. Rankings were compared within each receptor. Differences between proteins were not interpreted as established selectivity. Compound selection considered the score pattern, reported absorption limitations and completeness of the supporting records.

RESULTS

Complete docking matrix

The complete docking matrix is presented in Table 2 and Figure 1. Withaferin A and Ashwagandhanolide shared the lowest BChE score, while Withanolide D gave the lowest BACE1 score. Sitoindoside IX ranked first among phytochemicals against AChE, GSK3β and COX2. Donepezil retained a lower score than every phytochemical against AChE and COX2. Figure 2 shows selected BChE complex images from the source, and Figure 3 compares the reported BChE and BACE1 scores for the principal candidates.

Table 2: Reported Docking Scores in Kcal/Mol.

Compound	AChE	BChE	BACE1	GSK3β	COX2
Donepezil	−11.358	−9.611	−8.332	−8.478	−9.151
Rivastigmine	−7.703	−6.900	−6.520	−6.104	−6.838
Verubecestat	−11.283	−9.359	−8.779	−7.144	−7.629
Withaferin A	−9.422	−11.725	−10.592	−8.192	−6.150
Withanolide A	−10.868	−10.774	−10.551	−7.608	−8.044
Withanolide B	−10.183	−10.815	−9.699	−7.199	−7.349
Withanolide D	−9.649	−11.604	−10.670	−6.798	−6.833
Withanone	−8.533	−10.257	−9.662	−6.606	−6.612
Sitoindoside IX	−11.010	−11.314	−10.418	−8.634	−8.213
Sitoindoside X	−6.454	−9.684	−8.547	−4.343	−5.144
Somniferine	+0.189	−11.561	−9.529	−5.251	−5.103
Withanoside IV	−3.861	−11.681	−9.729	−7.524	−6.340
Withanoside V	−5.798	−11.391	−10.483	−6.129	−5.144
Ashwagandhanolide	+18.092	−11.725	−9.790	−6.524	−6.150
12 Deoxywithastramonolide	−10.312	−10.651	−9.776	−6.819	−5.606

Source: dissertation Table 4, page 42.[8] The first three compounds are comparators. A lower score means a more favourable prediction under the reported scoring procedure. The displayed three decimal places reproduce the source and do not imply experimental precision.

Cholinesterase results

All twelve phytochemicals have BChE scores below the donepezil value of −9.611 kcal/mol. The difference is only 0.073 kcal/mol for Sitoindoside X. It is therefore inappropriate to describe every compound as substantially better than the comparator. Against AChE, Sitoindoside IX gives −11.010 kcal/mol, followed by Withanolide A at −10.868 kcal/mol. Ashwagandhanolide and Somniferine give positive AChE scores. These require examination of the input geometry and search procedure before a structural explanation is accepted.

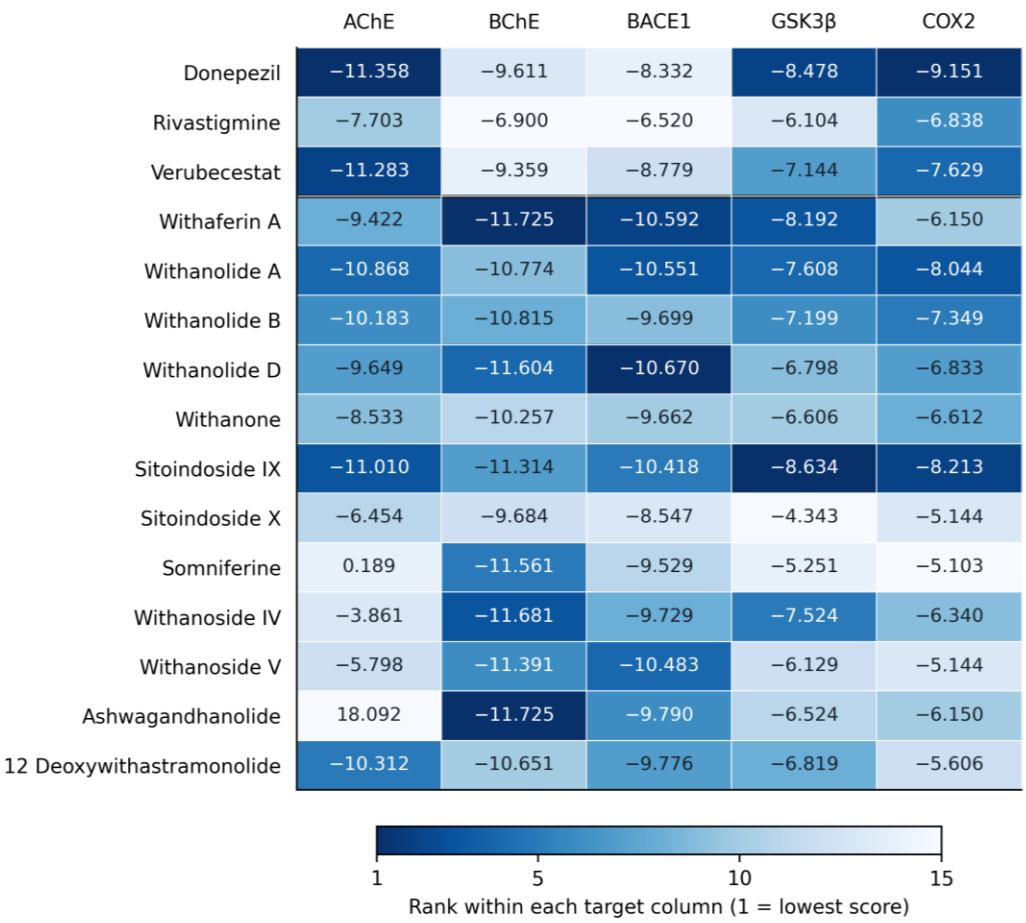


Figure: 1. Docking score matrix for fifteen compounds against five targets. Values reproduce Table 2 in kcal/mol. Colour represents rank within each target column, with darker cells indicating a lower score; tied values share a rank. The line separates reference compounds from phytochemicals. Colour does not establish selectivity between targets. Replotted from the dissertation data.[8]

Pharmacokinetic findings

Six phytochemicals were reported with zero Lipinski violations and high gastrointestinal absorption: Withaferin A, Withanolides A, B and D, Withanone and 12 Deoxywithastramonolide. Table 3 retains the source classifications as reported predictions. They remain provisional because the descriptor table contains identifiable inconsistencies. Withaferin A is listed at 456.57 g/mol in the dissertation[8], whereas PubChem CID 265237 gives 470.6 g/mol.[24] Correcting this descriptor does not retrospectively validate the structure submitted to either docking or ADME prediction.

Table 3: Reported Absorption and Drug Property Classifications for the Phytochemicals.

Compound	GI absorption	Brain prediction	Lipinski violations
Withaferin A	High	No	0
Withanolide A	High	No	0
Withanolide B	High	No	0
Withanolide D	High	No	0
Withanone	High	No	0
12 Deoxywithastramonolide	High	No	0
Sitoindoside IX	Low	No	2
Sitoindoside X	Low	No	2
Somniferine	High	No	1
Withanoside IV	Low	No	3
Withanoside V	Low	No	3
Ashwagandhanolide	63.82%	logBB −1.006	Not reported

Source: dissertation Table 5, pages 43 and 44.[8] The first eleven rows are attributed to SwissADME; the final row is attributed to pkCSM. "No" denotes a negative model classification, not an experimental demonstration of absent brain exposure. The absorption percentage and categorical outputs are not equivalent measurements.

The dissertation lists seven hydrogen bond acceptors for rivastigmine.[8], whereas PubChem CID 77991 reports three.[25] Its reported Lipinski violation cannot be reconciled simply from the displayed descriptors. The dissertation alternates between iLOGP and consensus LogP[8], although SwissADME reports these separately.[16] These discrepancies prevent confident reconstruction of the pharmacokinetic calculations from the dissertation alone.

For Ashwagandhanolide, the reported intestinal absorption is 63.82% and logBB is −1.006. The source reports negative hepatotoxicity and Ames predictions.[8] These are model classifications. They do not establish safety, and the logBB value does not prove that brain entry is completely blocked. The reported negative brain predictions across the phytochemicals remain a limitation to be examined experimentally.

BACE1, GSK3β and COX2 results

Withanolide D gives the lowest BACE1 score, at −10.670 kcal/mol. Withaferin A and Withanolide A follow at −10.592 and −10.551 kcal/mol. The Withanolide D value is 1.891 kcal/mol below that of verubecestat. This difference describes the reported scoring function; it does not establish stronger inhibition or superior suppression of amyloid production. The small differences between the three leading withanolides do not support a firm biological ranking without repeated calculations and assays.

Sitoindoside IX gives −8.634 kcal/mol against GSK3β, compared with −8.478 kcal/mol for donepezil and −8.192 kcal/mol for Withaferin A. A difference of 0.156 kcal/mol from donepezil cannot be assigned biological significance from a single score. Further, donepezil is not a dedicated GSK3β assay control. The deposited inhibitor AR A014418 provides a more relevant structural comparator for a repeated investigation.[3]

For COX2, Sitoindoside IX gives −8.213 kcal/mol and Withanolide A gives −8.044 kcal/mol. Both are less favourable than the reported donepezil score of −9.151 kcal/mol. The Withaferin A score is −6.150 kcal/mol. None of these values demonstrates reduced inflammation. Meclofenamic acid is the deposited inhibitor in 5IKQ and should be distinguished from the three compounds included in the screening matrix.[4]

Target prediction and network findings

The source reports SwissTargetPrediction outputs of 0.109 for Withaferin A with AChE, 0.113 for Withanolide D with COX2, 0.094 for Withanoside IV with the muscarinic M1 receptor, and 0.086 for Sitoindoside IX with GSK3β.[8] These values should not be read as measurements of affinity. The target class pie charts describe the composition of predicted target lists; class percentages do not establish the probability of kinase inhibition or another biological response.

The Ashwagandhanolide record is internally inconsistent. The summary table lists the glucocorticoid receptor at 0.82, whereas the narrative identifies cathepsin D at 95.7% as the leading target and lists additional predictions for NFκB p105, cannabinoid CB2 receptor, ADAM10 and other proteins.[8] Without the original SuperPred export, a definitive target ranking cannot be reconstructed. The present interpretation therefore makes no claim that Ashwagandhanolide engages several disease pathways simultaneously.

Withaferin A and Sitoindoside IX are described as highly connected in the source network.[8] Exact centrality values are absent, and the text gives conflicting accounts of whether Ashwagandhanolide was included. Enrichment is reported for processes related to amyloid, tau, inflammation and synaptic transmission, but term identifiers, background sets and adjusted probabilities are unavailable. These observations provide qualitative context only. Statistical enrichment and the proposed hub ordering cannot be independently confirmed.

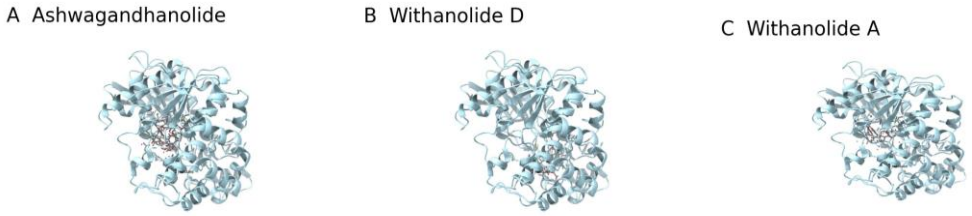


Figure: 2. Source illustrations of BChE complexes, identified in the dissertation as (A) Ashwagandhanolide, (B) Withanolide D and (C) Withanolide A, using PDB 4BDS. Protein ribbons and ligand sticks are reproduced from dissertation pages 37 and 38.[8] Panels are illustrative; original coordinates were unavailable to verify pose identity, residue contacts or distances. No new docking images are implied.

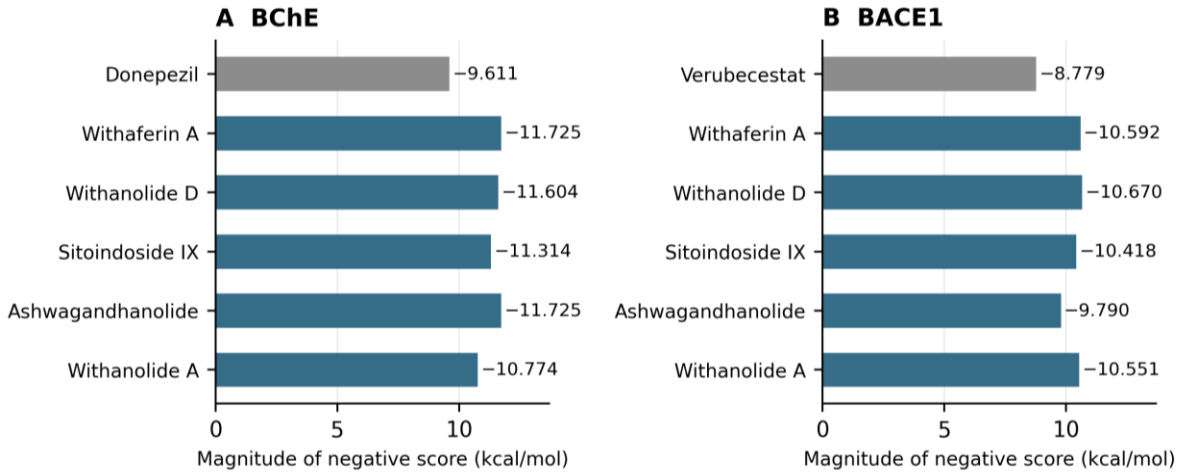


Figure: 3. Reported scores for selected phytochemicals and a reference compound against (A) BChE and (B) BACE1. Bar lengths show the magnitude of the negative score; labels retain the signed value in kcal/mol. Grey bars denote donepezil and verubecestat, respectively. Each value is one reported result, so no error bars or statistical significance are shown. Replotted from Table 2.[8]

DISCUSSION

What the docking pattern supports

BChE showed the most consistent favourable scoring pattern within the phytochemical set. Withaferin A and Ashwagandhanolide shared the minimum, followed by Withanoside IV and Withanolide D. The source complex images place the displayed ligands within the protein framework (Figure 2), but do not provide sufficient detail to confirm individual residue contacts. The score comparison supports a repeated BChE screen of the selected compounds (Figure 3). It does not establish inhibition or superiority to an approved medicine.

A wider binding cavity may accommodate a bulky ligand more readily than a narrower cavity. However, the positive AChE score for Ashwagandhanolide cannot, by itself, demonstrate steric exclusion. Incorrect starting coordinates, unsuitable protonation, a restrictive search box or insufficient sampling can also produce an unfavourable result. The difference between its AChE and BChE scores should therefore be treated as a question for structural examination, rather than a proven selectivity mechanism. Cholinesterase structures show why receptor identity and ligand orientation deserve direct attention.[9,10]

Choice of compounds for further work

Withaferin A and Withanolide D merit early reassessment. The first shares the lowest BChE score and has a favourable BACE1 score. The second has the lowest BACE1 score and a favourable BChE score. Their reported absorption profiles are more convenient than those of the glycosides, although the Withaferin A descriptor error must be resolved before using ADME results to choose between them. Neither molecule can presently be described as clinically translatable on this evidence.

Sitoindoside IX merits retention because of its ranking across the panel. It is first among phytochemicals for three receptors and scores favourably for BChE and BACE1. Its reported low gastrointestinal absorption and two Lipinski violations create a separate question concerning exposure. The broad score pattern is useful for choosing assays, but there is no universal docking threshold by which it becomes a confirmed molecule acting on multiple targets.

Ashwagandhanolide is a conditional candidate. Its BChE score is favourable, but its large structure, anomalous AChE result and unresolved target predictions require further checking. The immediate requirement is confirmation of molecular identity and repeat docking. Formulation development would be premature before biological activity and exposure are established. A delivery system cannot be assumed to correct every pharmacokinetic limitation.

Withanolide A should also remain in the comparison set. It performs consistently across the five columns and ranks close to Sitoindoside IX against AChE and COX2. Its prior experimental record includes neuritic and synaptic effects.[5] That evidence does not validate the present docking poses, but it provides a sound reason to retain the molecule. The

available results do not justify an exclusive four compound shortlist that discards this comparator.

Biological interpretation and limitations

Plant extracts, isolated constituents and metabolites need separate consideration. The hepatic mechanism described for a Withania extract suggests that peripheral processes may also contribute to biological effects.[6] Direct action at a central target nevertheless requires adequate exposure. The present predictions do not establish that requirement.

The BACE1 scores require clinical perspective. Verubecestat did not improve outcomes in prodromal Alzheimer's disease, and some measures were worse in treated participants.[26] A docking score below that of verubecestat therefore cannot demonstrate clinical superiority.

The main limitations concern reproducibility and biological validation. Exact docking grids, random seeds, receptor chains, prepared ligand structures and individual redocking deviations were unavailable. Descriptor inconsistencies and incomplete target prediction exports require resolution. Molecular dynamics, binding free energy calculations and experimental assays were not part of the available record. Agreement between docking and target prediction is not independent experimental validation.

Further work should confirm input identities, repeat docking with the deposited reference ligands and report numerical pose deviations. Enzyme assays should include controls for solubility, interference and cytotoxicity. Exposure and metabolite studies are then needed to assess the proposed mechanism. Network enrichment requires a complete target list, a stated background and correction for multiple comparisons.

CONCLUSION

The reported scores identify Withaferin A, Withanolide D, Sitoindoside IX and Ashwagandhanolide as preliminary candidates for further evaluation, with Withanolide A retained as a comparator. Uncertain reproducibility and unfavourable predicted brain exposure remain the principal limitations. The findings support further investigation, but do not establish efficacy against Alzheimer's disease.

DECLARATIONS

Ethics approval and consent to participate. This computational study involved no human participants, identifiable human data, animal experiments or biological specimens. Ethics approval and participant consent are not applicable to the work described.

Consent for publication. Not applicable. The manuscript contains no identifiable participant information or images.

Author contributions. Md Tanweer Kausar carried out the investigation. Priyanka Srivastava prepared the original draft and revised and edited the manuscript. Satish Kumar Sarankar supervised the study.

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Competing interests. The authors declare that they have no competing interests.

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