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RESEARCH PAPER

In Silico molecular docking evaluation of mangiferin against key colorectal cancer associated proteins

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ABSTRACT

Colorectal cancer (CRC) is a multifactorial malignancy driven by dysregulated inflammatory signaling, aberrant cell proliferation, defective apoptosis, loss of tumor suppressor functions, and aberrant activation of oncogenic signaling pathways. The identification of multi-target agents capable of simultaneously modulating these interconnected pathways represents a promising therapeutic strategy. In the present study, the multi-target therapeutic potential of mangiferin, a bioactive C-glucosyl xanthone, was systematically evaluated against key CRC-associated molecular targets using structure-based molecular docking. Molecular docking was performed using AutoDock Vina against proteins involved in inflammation (TNF-α and COX-2), proliferation and angiogenesis (K-Ras, BRAF, β-catenin, VEGFR-2, and Cyclin D1), apoptosis (Bcl-2, BAX, and Caspase-3), tumor suppression (p53 and APC), and the PI3K/Akt/mTOR signaling pathway (PI3K-α, AKT, and mTOR). Protein structures were retrieved from the RCSB Protein Data Bank and docked following binding-site prediction using CASTp. Mangiferin exhibited strong to moderate binding affinities toward all selected targets, with docking scores ranging from −10.5 to −7.0 kcal/mol. The strongest binding affinity was observed with TNF-α (−10.5 kcal/mol), followed by AKT (−10.3 kcal/mol), COX-2 (−9.8 kcal/mol), BRAF (−9.4 kcal/mol), and PI3K-α (−9.4 kcal/mol), indicating effective targeting of inflammatory mediators and oncogenic survival signaling pathways. Moderate binding affinities were observed for VEGFR-2 and p53 (−8.5 kcal/mol), K-Ras and APC (−8.4 kcal/mol), and Bcl-2 (−8.2 kcal/mol), suggesting potential inhibition of angiogenesis, cell proliferation, and anti-apoptotic signaling. Additionally, mangiferin demonstrated favorable interactions with β-catenin (−7.7 kcal/mol), caspase-3 (−7.6 kcal/mol), mTOR (−7.5 kcal/mol), BAX (−7.1 kcal/mol), and Cyclin D1 (−7.0 kcal/mol), highlighting its capacity to modulate Wnt signaling, apoptosis, cell-cycle regulation, and PI3K/AKT/mTOR pathway components. Overall, mangiferin–protein complexes were stabilized through a combination of hydrogen bonding and hydrophobic π-interactions, supporting mangiferin as a promising multi-target phytochemical with therapeutic relevance in colorectal cancer.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent malignancies and remains a leading cause of cancer-related mortality worldwide. In India, CRC ranks as the fourth most commonly diagnosed cancer in both sexes, with 64,863 new cases and 38,367 deaths reported in 2022 (Ferlay *et al.*, 2024). Despite substantial advances in diagnostic techniques and therapeutic strategies, the overall survival rate of CRC patients in India remains considerably lower than that reported in developed countries. While several Western nations have experienced a gradual decline in CRC incidence, many regions of India continue to show an alarming upward trend, with significantly higher incidence rates observed in urban populations compared with rural regions (Shivshankar *et al.*, 2025).

Natural bioactive compounds have gained increasing attention as potential anticancer agents due to their multi-target properties and favorable safety profiles. Mangiferin (Fig. 1), a C-glucosyl xanthone predominantly isolated from Mangifera indica L., is widely consumed as both a traditional medicinal agent and a dietary component across various cultures. Extensive pharmacological studies have demonstrated that mangiferin exhibits a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, and anticancer effects against lung, prostate, ovarian, and breast cancers (Du *et al.*, 2018; Imran *et al.*, 2017; Rahmani *et al.*, 2023). At the mechanistic level, mangiferin has been reported to suppress oxidative stress and inflammatory mediators, inhibit cancer cell proliferation, and induce apoptosis during carcinogenesis (Vishwanadha Vijaya Padma *et al.*, 2015). These effects suggest that mangiferin may function as a multi-target modulator of key oncogenic pathways implicated in colorectal cancer progression.

Colorectal cancer initiation and progression arise from a complex network of molecular alterations involving the dysregulation of inflammatory, proliferative, apoptotic, and tumour suppressor signalling pathways (Li *et al.*, 2024). Persistent inflammatory signalling, primarily mediated by pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), establishes a tumour-promoting microenvironment characterized by oxidative stress, DNA damage, and uncontrolled cellular proliferation (Kumar *et al.*, 2024; Brücher *et al.*, 2019).

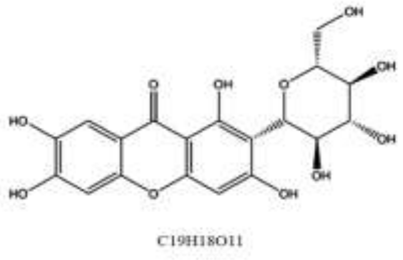

Fig. 1. Structure of mangiferin

Cyclooxygenase-2 (COX-2) functions as a critical molecular link between chronic inflammation and tumour progression and is markedly overexpressed in colorectal carcinomas. Upregulation of COX-2 leads to enhanced prostaglandin E2 (PGE2) synthesis, which drives tumour cell proliferation, angiogenesis, and survival through the activation of multiple oncogenic signalling cascades (Desai *et al.*, 2018). Concomitantly, aberrant activation of key proliferative and angiogenic mediators, including vascular endothelial growth factor receptor-2 (VEGFR-2) (Lešnik *et al.*, 2021), BRAF (Talloa *et al.*, 2022), Cyclin D1 (Maggisano *et al.*, 2017), K-Ras, and β-catenin (Clark *et al.*, 2011), promotes uncontrolled cell cycle progression, enhanced survival signalling, and neovascularization. In addition, disruption of apoptotic homeostasis through altered expression of B-cell lymphoma-2 (Bcl-2), Bcl-2-associated X protein (BAX), and Caspase-3 impairs programmed cell death, thereby facilitating tumour cell persistence and therapeutic resistance (Naseri *et al.*, 2015).

Furthermore, loss or functional inactivation of tumour suppressor genes, notably tumour protein p53 (p53) and adenomatous polyposis coli (APC), accelerates genomic instability and constitutive activation of the Wnt/β-catenin pathway, ultimately reinforcing the malignant phenotype of colorectal epithelial cells (Ruban *et al.*, 2025).

The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway plays a pivotal role in regulating cell growth, metabolism, proliferation, survival, and angiogenesis in both normal and cancer cells (Karar and Maity 2011). Aberrant activation of the PI3K/Akt/mTOR axis is one of the most frequently observed molecular alterations in CRC and is strongly associated with tumour initiation, progression, invasion, and metastasis. Persistent stimulation of this pathway promotes uncontrolled cell survival while inhibiting apoptosis, thereby contributing to aggressive tumour phenotypes (Leiphrakpam and Are 2024). Importantly, dysregulation of PI3K/Akt/mTOR signaling has been closely linked to the development of drug resistance, limiting the effectiveness of conventional chemotherapeutic and targeted therapies (Dong *et al.*, 2021). Consequently, several inhibitors targeting PI3K, Akt, and mTOR either alone or in combination are currently under clinical investigation for CRC treatment, highlighting the therapeutic relevance of this pathway.

Given this multifaceted molecular landscape, the identification of small molecules capable of simultaneously targeting inflammatory mediators, proliferative kinases, apoptotic regulators, and tumour suppressor pathways represents an attractive and rational therapeutic strategy for colorectal cancer management. However, despite the growing evidence supporting mangiferin's anticancer potential, the structural basis underlying its interaction with key colorectal cancer-associated molecular targets remains incompletely understood. Molecular docking serves as a robust in silico approach for predicting ligand–protein binding conformations, interaction patterns, and binding affinities within active or regulatory sites of target proteins (Chaudhary *et al.*, 2024). AutoDock Vina, a widely used structure-based virtual screening tool (Baba *et al.*, 2011), was employed in the present study to systematically dock mangiferin against colorectal cancer-relevant inflammatory, proliferative, apoptotic, and tumour suppressor proteins (Fig. 2). Through comprehensive binding affinity and interaction analysis, this study aims to elucidate the multi-target interaction profile of mangiferin and to provide molecular insights supporting its therapeutic potential in colorectal cancer development and progression.

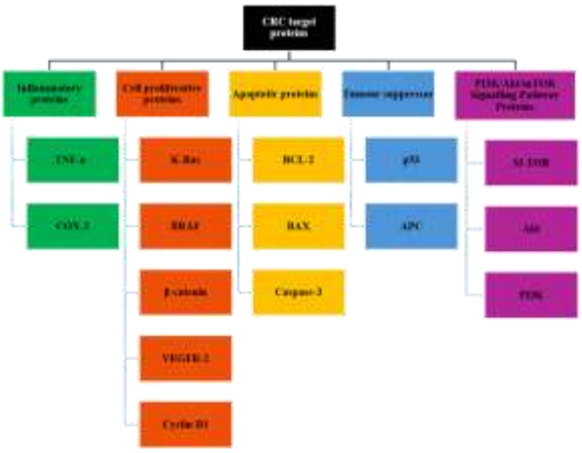

Fig. 2. Targeted proteins associated with colorectal cancer

MATERIALS AND METHODS

Ligand preparation

The three-dimensional structure of mangiferin (PubChem ID: 5281647) was retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov/), which provides curated structural information for small molecules (Ragunathan *et al.*, 2022). The ligand structure was imported into PyMOL for visualization and preliminary modification and subsequently prepared for molecular docking by exporting it in Protein Data Bank (PDB) format (Seeliger *et al.*, 2010). Final conversion of the ligand into the PDBQT format required for docking was carried out using MGL Tools, ensuring appropriate atom type assignment, definition of rotatable bonds, and accurate charge distribution (Forli *et al.*, 2016).

Protein preparation

PDB structures of colorectal cancer associated target proteins were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/) (Begum *et al.*, 2024). The selected inflammatory targets included tumour necrosis factor-α (TNF-α; PDB ID: 1TNF). Cell proliferative and angiogenic targets comprised K-Ras (PDB ID: 5US4), BRAF (PDB ID: 4R5Y), β-catenin

(PDB ID: 6M93), vascular endothelial growth factor receptor-2 (VEGFR-2; PDB ID: 2OH4), and Cyclin D1 (PDB ID: 2W96). Apoptotic regulators included Bcl-2 (PDB ID: 2W3L), BAX (PDB ID: 4S0O), and Caspase-3 (PDB ID: 5I9B), while tumour suppressor proteins included p53 (PDB ID: 3DCY) and adenomatous polyposis coli (APC; PDB ID: 3NMZ). All protein structures were prepared by removing co-crystallized ligands, water molecules, and non-essential chains. Subsequently, polar hydrogens were added and Kollman or compatible force-field charges were assigned using AutoDock Tools implemented in the MGL Tools suite, following a standard protein preparation workflow (Gimeno *et al.*, 2020).

Binding site prediction

The Computed Atlas of Surface Topography of Proteins CASTp server was employed to identify potential ligand binding sites on each target protein by analysing solvent accessible surface pockets and interior cavities derived from their three dimensional structures (Tian *et al.*, 2018). For each protein, the top ranked pocket characterized by the largest volume and surface area and corresponding to a known functional region was selected as the docking site.

The centre of the docking grid was defined using the geometric centroid of the selected cavity (Feinstein *et al.*, 2015). Grid box dimensions were subsequently adjusted to fully encompass the active site pocket and neighbouring residues, thereby ensuring sufficient space for ligand flexibility, orientation, and comprehensive conformational sampling during molecular docking.

Molecular docking and interaction analysis

AutoDock Vina was employed to dock mangiferin into each target protein. For each protein, the docking pose with the lowest predicted binding energy was selected as the most stable protein ligand complex. Docking was performed using default exhaustiveness parameters, with the receptor maintained in a rigid state while allowing full ligand flexibility. Protein ligand interactions of the top ranked poses were analysed using BIOVIA Discovery Studio Visualizer, with emphasis on hydrogen bonding, hydrophobic interactions, and other relevant non covalent interactions. These interactions were documented using two dimensional and three dimensional binding site representations (Haque *et al.*, 2022; Rahman *et al.*, 2021).

RESULTS

The molecular docking analysis demonstrated strong to moderate binding affinities of mangiferin toward all eleven selected colorectal cancer–associated target proteins, with predicted binding energies ranging from −7.0 to −10.5 kcal/mol (Table 1).

Table 1. Binding affinity and key stabilizing interactions of Mangiferin with CRC- associated target proteins

Protein (PDB ID)	Binding affinity (kcal/mol)	Key strong interactions observed
TNF-α (1TNF)	−10.5	Conventional hydrogen bond, π–anion
BRAF (4R5Y)	−9.4	Conventional hydrogen bond, π–stacked, π–alkyl
VEGFR-2 (2OH4)	−8.5	Conventional hydrogen bond, π–sigma, π–alkyl
p53 (3DCY)	−8.5	Conventional hydrogen bond, π–cation, π–donor hydrogen bond
K-Ras (5US4)	−8.4	Conventional hydrogen bond, π–cation, π–T-shaped, π–alkyl
APC (3NMZ)	−8.4	Conventional hydrogen bond, π–cation, π–alkyl
Bcl-2 (2W3L)	−8.2	Conventional hydrogen bond, π–donor hydrogen bond, π–T-shaped, π–alkyl
β-Catenin (6M93)	−7.7	Conventional hydrogen bond, π–cation
Caspase-3 (5I9B)	−7.6	Conventional hydrogen bond, π–anion, π–π T-shaped
BAX (4S0O)	−7.1	Conventional hydrogen bond, π–donor hydrogen bond, π–alkyl
Cyclin D1 (2W96)	−7.0	Conventional hydrogen bond, π–sigma
m-TOR	−7.5	Conventional hydrogen bond, carbon hydrogen bond, π–alkyl
AKT	−10.3	Conventional hydrogen bond, π–π stacked, π–sigma, π–alkyl
COX-2	−9.8	Conventional hydrogen bond, carbon hydrogen bond, π–alkyl
PI3K ALPHA	−9.4	Conventional hydrogen bond, π–alkyl

In addition to favorable binding energies, mangiferin established multiple stabilizing interactions within the active sites of the target proteins, predominantly through conventional hydrogen bonds along with π–π stacking, π–cation, π–anion, π–sigma, and π–alkyl interactions. These interactions contribute significantly to ligand stabilization and binding specificity, indicating the multi-target inhibitory potential of mangiferin against key colorectal cancer–related signaling proteins.

Docking with inflammatory target

Mangiferin showed strong binding affinity toward inflammatory proteins involved in colorectal cancer progression. The highest binding affinity was observed with TNF-α (−10.5 kcal/mol), indicating stable binding within the predicted active site. Mangiferin also exhibited significant affinity toward COX-2 (−9.8 kcal/mol), suggesting stable interactions within its catalytic domain. The ligand–protein complexes were mainly stabilized by hydrophobic interactions and conventional hydrogen bonds (Fig. 3).

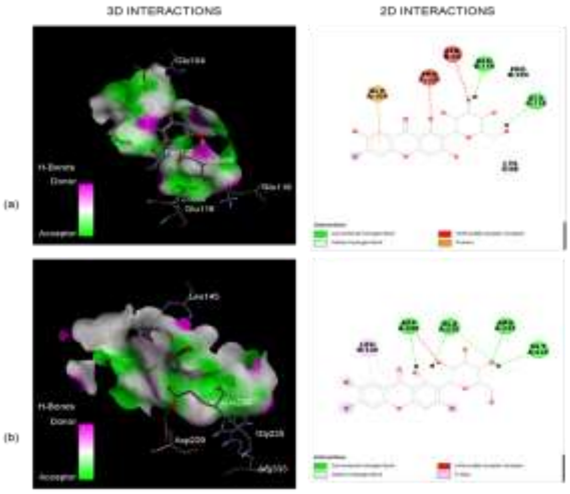

Fig. 3. 3D and 2D interaction profiles of mangiferin with inflammatory proteins: (a) TNFα (1TNF) (b)COX-2

Docking with proliferation associated proteins

Mangiferin effectively docked with cell proliferation and angiogenesis related proteins, including K Ras, BRAF, β catenin, VEGFR 2, and Cyclin D1. Among these targets, BRAF showed the strongest binding affinity (−9.4 kcal/mol), followed by VEGFR 2 (−8.5 kcal/mol) and K Ras (−8.4 kcal/mol). β catenin and Cyclin D1 exhibited binding energies of −7.7 and −7.0 kcal/mol, respectively (Fig. 4AandB).

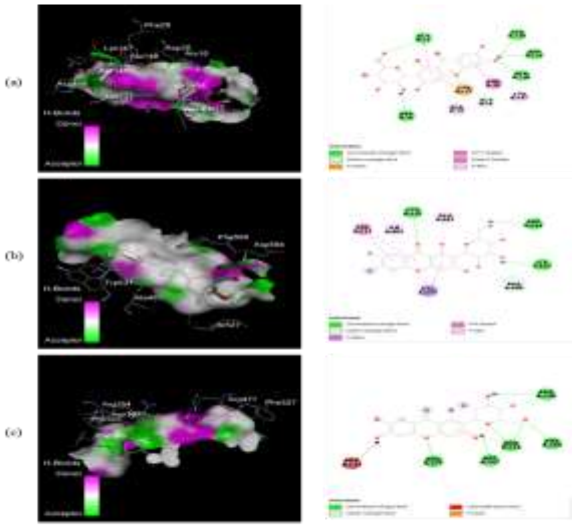

Fig. 4A. 3D and 2D interaction profiles of mangiferin with proliferation related proteins: (a) K Ras (5US4), (b) BRAF (4R5Y), (c) β catenin (6M93), (d) VEGFR 2 (2OH4), and (e) Cyclin D1 (2W96)

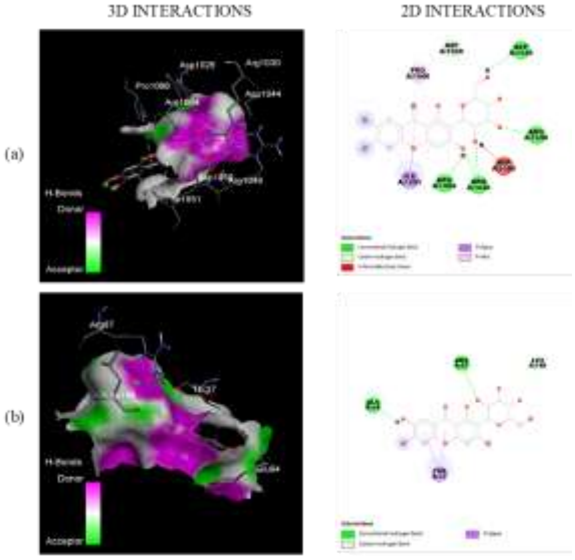

Fig. 4B. 3D and 2D interaction profiles of mangiferin with proliferation related proteins: (a) VEGFR 2 (2OH4), and (b) Cyclin D1 (2W96)

Docking with apoptotic regulators

Mangiferin demonstrated moderate to strong binding affinities toward apoptotic regulatory proteins Bcl 2, BAX, and Caspase 3 with docking energies of −8.2, −7.1, and −7.6 kcal/mol, respectively (Fig. 5).

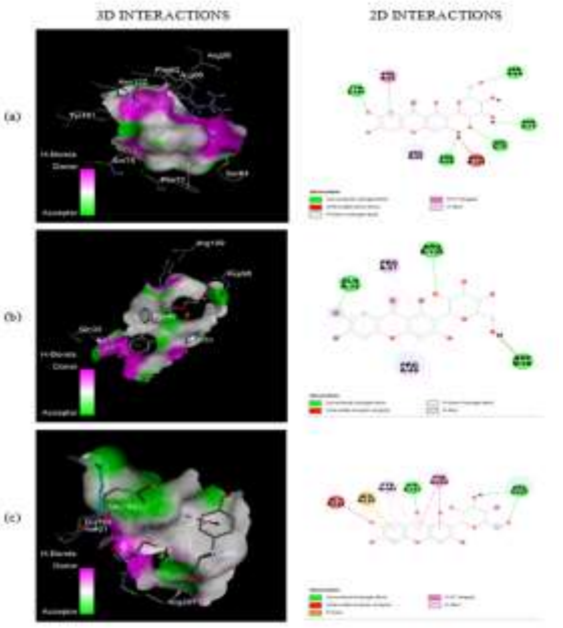

Fig. 5. 3D and 2D interaction profiles of mangiferin with apoptotic regulatory proteins: (a) Bcl 2 (2W3L), (b) BAX (4S0O), and (c) Caspase 3 (5I9B)

Docking with tumour suppressor proteins

Mangiferin exhibited favourable docking interactions with tumour suppressor proteins p53 and APC, showing binding energies of −8.5 and −8.4 kcal/mol, respectively (Fig. 6).

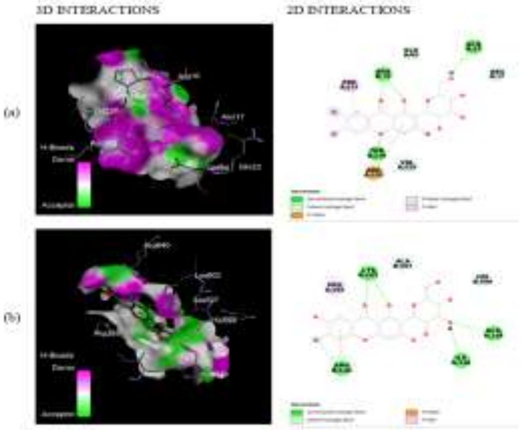

Fig. 6. 3D and 2D interaction profiles of mangiferin with tumor suppressor proteins: (a) p53 (3DCY) and (b) APC (3NMZ)

PI3K/Akt/m-TOR signalling pathway proteins

Mangiferin exhibited strong binding affinities toward key PI3K AKT mTOR pathway proteins (Fig. 7). The highest affinity was observed for AKT (−10.3 kcal/mol), followed by PI3K alpha (−9.4 kcal/mol) and mTOR (−7.5 kcal/mol). The interactions were primarily stabilized by conventional hydrogen bonds and hydrophobic interactions, including π-alkyl, π-π stacking, and π-sigma contacts. Overall, stronger binding affinities for AKT and PI3K alpha indicate more stable interactions within the PI3K AKT mTOR signaling pathway.

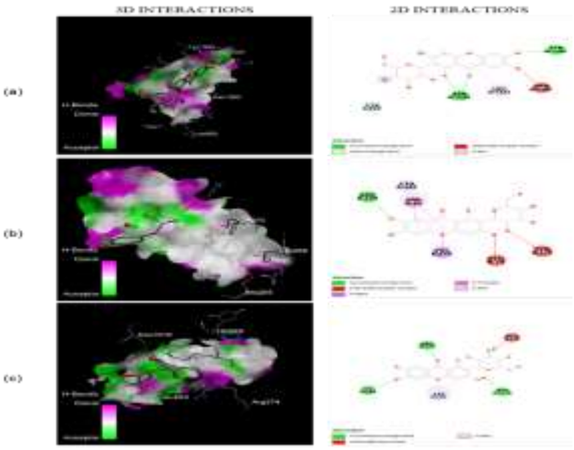

Fig. 7. 3D and 2D interaction profiles of mangiferin with tumor suppressor proteins: (a) m-TOR (6ZWM), (b) Akt (3O96) and (c) PI3K (7PG5)

DISCUSSION

The present molecular docking analysis highlights mangiferin as a promising phytoconstituent with strong to moderate binding affinities toward multiple colorectal cancer (CRC) associated molecular targets involved in inflammation, proliferation, angiogenesis, apoptosis, and tumor suppression. The ability of mangiferin to interact with diverse signaling proteins underscores its multi target therapeutic potential, which is particularly relevant for CRC.

Chronic inflammation is a key contributor to colorectal carcinogenesis. Among the inflammatory mediators analyzed, mangiferin exhibited the strongest binding affinity toward TNF α, a central regulator of inflammation driven tumorigenesis. TNF α promotes NF κB activation, oxidative stress, angiogenesis, and the establishment of a tumor promoting microenvironment in CRC (Wu *et al.*, 2019; Khan *et al.*, 2025). The strong stabilization of mangiferin within the TNF α binding site suggests its potential to suppress inflammation mediated oncogenic signaling and attenuate CRC progression. In addition, mangiferin demonstrated significant affinity toward cyclooxygenase 2 (COX 2), a pro inflammatory enzyme frequently overexpressed in CRC. COX 2 mediated prostaglandin synthesis drives chronic inflammation, cell proliferation, angiogenesis, and resistance to apoptosis (Pang *et al.*, 2016). Stable interactions of mangiferin within the catalytic domain of COX 2, supported by hydrogen bonding and hydrophobic interactions, indicate a potential inhibitory effect on COX 2 activity. The concurrent targeting of TNF α and COX 2 suggests effective modulation of inflammation associated carcinogenic signaling.

Mangiferin also exhibited strong binding affinities toward key proteins involved in CRC associated proliferative signaling, including BRAF, K Ras, VEGFR 2, β catenin, and Cyclin D1, indicating interference with multiple growth promoting pathways. Aberrant activation of the RAS RAF MEK ERK cascade, primarily driven by mutations in K Ras and BRAF, is a hallmark of CRC and results in sustained proliferative signaling and resistance to apoptosis (Yen *et al.*, 2018; Bahar *et al.*, 2023). Strong interactions with BRAF and stable binding to K Ras suggest disruption of kinase activity or regulatory interactions, thereby suppressing downstream mitogenic signaling. Favorable binding to β catenin and VEGFR 2 further indicates the ability of mangiferin to inhibit Wnt β catenin mediated transcription and angiogenic signaling, both of which are critical for tumor growth and metastasis (Paul *et al.*, 2021). Binding to Cyclin D1 supports a role in regulating cell cycle progression through induction of G1 S phase arrest, slowdown uncontrolled proliferation (Lecarpentier *et al.*, 2019). The apoptotic regulatory network represents another important therapeutic target in CRC.

Mangiferin exhibited stable and energetically favorable binding interactions with the anti apoptotic protein Bcl 2 as well as the pro apoptotic proteins BAX and Caspase 3, indicating modulation of mitochondrial mediated apoptosis. Overexpression of Bcl 2 is associated with apoptosis resistance and chemoresistance in CRC (Kang *et al.*, 2009; Vogler *et al.*, 2025).

Binding of mangiferin to Bcl 2 may disrupt Bcl 2 BAX heterodimer formation, restoring mitochondrial outer membrane permeabilization. Concurrent binding to BAX supports its activation and mitochondrial translocation, while interaction with Caspase 3 suggests enhanced execution of apoptosis. These findings are consistent with previous experimental studies reporting mangiferin induced mitochondrial depolarization, cytochrome c release, and Caspase 3 activation (Abotaleb *et al.*, 2018; Peña Blanco *et al.*, 2018; Mustafa *et al.*, 2024).

Mangiferin also showed strong affinity toward the tumor suppressor proteins p53 and APC, which are critical regulators of genomic stability and cell fate. Mutation or loss of APC is an early event in CRC, leading to aberrant β catenin accumulation and adenoma formation (Cho *et al.*, 2020), while p53 dysfunction impairs DNA damage response and apoptotic signaling (Hernández Borrero *et al.*, 2021). Simultaneous docking of mangiferin to APC and β catenin suggests reinforcement of β catenin degradation and suppression of Wnt driven tumorigenesis. In addition, favorable binding to p53 may stabilize transcriptionally active conformations, enhancing tumor suppressive functions such as cell cycle arrest, DNA repair, and apoptosis (Marcolino *et al.*, 2020).

Furthermore, mangiferin exhibited strong binding affinities toward key components of the PI3K AKT mTOR signaling axis, including AKT, PI3K alpha, and mTOR. Dysregulation of this pathway promotes cell survival, proliferation, metabolic reprogramming, angiogenesis, and therapeutic resistance in CRC (Narayanankutty, 2019). Mangiferin showed the highest affinity toward AKT, followed by PI3K alpha and mTOR, indicating preferential targeting of upstream survival signaling nodes. These interactions, stabilized by hydrogen bonds and hydrophobic contacts, suggest effective inhibition of PI3K, AKTmediated signaling and downstream mTOR driven protein synthesis. Consequently, suppression of this pathway may reduce proliferative and survival advantages of CRC cells while enhancing apoptotic sensitivity.

Overall, the strong interactions of mangiferin with inflammatory mediators, oncogenic kinases, apoptotic regulators, and tumor suppressor proteins highlight its multi pathway inhibitory potential. These in silico findings provide strong mechanistic support for further *in vitro* and *in vivo* studies to validate the chemopreventive and therapeutic potential of mangiferin against colorectal cancer.

CONCLUSION

The docking results identify mangiferin as a promising multitarget phytoconstituent with consistent binding across inflammatory mediators, proliferative regulators, apoptotic effectors, and tumour suppressor proteins implicated in colorectal cancer. Its strong affinity toward TNF α highlights potential upstream modulation of inflammation, while interactions with BRAF, K Ras, VEGFR 2, and β catenin suggest disruption of key oncogenic signalling pathways. Concurrent engagement of apoptotic and tumour suppressor proteins further supports the ability of mangiferin to restore cellular homeostasis and suppress malignant progression. These findings provide a strong computational rationale for further experimental validation of mangiferin as a therapeutic candidate for colorectal cancer.

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