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In Vitro Herb Drug Pharmacokinetic Interaction Study of 5 Fluorouracil (5-FU) with Turmacin

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ABSTRACT

Background: Herbal supplements are frequently used with anticancer chemotherapy, prompting worries over clinically significant herb–drug interactions. Turmacin®, a polysaccharide-rich aqueous extract of Curcuma longa, exhibits mucilage-forming, immunomodulatory, and antioxidant characteristics that may affect medication absorption and metabolism. 5-Fluorouracil (5-FU), a hydrophilic chemotherapy drug characterized by limited and variable absorption, is notably influenced by herbal components.

Objective: The objective of this study is to examine the in-vitro pharmacokinetic interaction between Turmacin and 5-FU by various mechanistic models, encompassing phytochemical profiling, physicochemical analysis, Caco-2 permeability, and P-glycoprotein (P-gp) ATPaseassays.

Methods: The standardized Turmacin extract was analyzed for its phytochemical and physicochemical properties. Caco-2 monolayers were employed to assess bidirectional permeability (AP→BL and BL→AP) of 5-FU, with or without Turmacin (200 µg/mL). Transporter interaction was evaluated utilizing human P-glycoprotein membrane vesicles using ATPase activity experiments. Physicochemical and phytochemical profiling encompassed assessments of acid value, ash content, melting point, soluble extractives, and the detection of flavonoids, tannins, alkaloids, essential oils, and antioxidants.

Results: Turmacin markedly diminished the AP→BL permeability of 5-FU by approximately 32%, while augmenting BL→AP efflux and raising the efflux ratio by around 41%, signifying improved P-gp–mediated transport. The ATPase assay indicated reduced inorganic phosphate release in the presence of Turmacin, implying partial inhibition of ATP hydrolysis and alteration of P-gp functionality. Phytochemical screening verified the existence of many beneficial compounds, whilst physicochemical examination demonstrated elevated purity, thermal stability, and hydrophilicity. In summary, diminished absorptive transport, augmented efflux, and heightened microsomal degradation all signify impaired availability of 5-FU in the presence of Turmacin

Conclusion: Turmacin significantly modifies the in-vitro pharmacokinetic properties of 5-FU by diminishing intestinal permeability, regulating efflux transporter activity, and increasing metabolic breakdown. These findings underscore a notable herb–drug interaction that may diminish the systemic absorption of 5-FU. Patients are urged to exercise caution when taking turmeric-based supplements during 5-FU treatment, and additional in-vivo studies are necessary to confirm these findings.

Keywords: *5-Fluorouracil, Turmacin, Herb-drug interaction, Caco-2 permeability, P-glycoprotein, Polysaccharides, Pharmacokinetics*

1. INTRODUCTION

Herbal supplements and plant-derived polysaccharides are increasingly utilized in conjunction with standard anticancer chemotherapy, prompting significant concerns about herb-drug interactions that may modify a drug's pharmacokinetic properties, including absorption, distribution, metabolism, and elimination [1,2]. These interactions arise because herbal extracts frequently comprise intricate combinations of bioactive compounds that might influence intestine transporters, metabolic enzymes, membrane permeability, and physiological mechanisms regulating drug disposition. Curcuma longa has gained significant interest among the different botanicals utilized in complementary medicine due to its extensive pharmacological qualities and broad therapeutic applications across cultures. Turmacin®, a proprietary aqueous extract of Curcuma longa, is fortified with turmerosaccharides (>10% w/w), a category of water-soluble polysaccharides that differ from the well studied curcuminoids. These turmerosaccharides exhibit proven anti-inflammatory, mucilage-forming, viscoelastic, immunomodulatory, and antioxidant properties, which may individually or jointly influence gastrointestinal physiology and pharmacokinetic processes [4–6]. Herbal extracts abundant in polysaccharides, such as Turmacin, are.

recognized for their capacity to affect intestinal permeability by creating viscous layers on the mucosal surface, prolonging gastric emptying, altering tight-junction functionality, and modifying unstirred water layers, which may consequently diminish drug diffusion and carrier-mediated absorption [7]. Moreover, specific plant polysaccharides and polyphenols have demonstrated the ability to regulate efflux transporters, including P-glycoprotein (P-gp), multidrug resistance proteins (MRPs), and breast cancer resistance protein (BCRP), in addition to metabolic enzymes such as cytochrome P450 (CYP) isoforms and uridine diphosphate glucuronosyltransferases (UGTs) [8,9]. The biochemical and biophysical alterations may significantly influence the pharmacokinetics of concurrently delivered conventional chemotherapeutic agents, especially those with limited therapeutic indices. 5-Fluorouracil (5-FU), a structurally uncomplicated pyrimidine antimetabolite, continues to be a fundamental component of chemotherapy protocols for colorectal, breast, gastrointestinal, and head-and-neck malignancies [10]. Notwithstanding its therapeutic efficacy, 5-FU is characterized by inadequate and extremely inconsistent oral bioavailability, mostly because to fast first-pass metabolism facilitated by dihydropyrimidine dehydrogenase (DPD) and considerable transporter-mediated efflux from the intestinal epithelium [11,12]. Due to its limited permeability and high sensitivity to enzymatic breakdown, 5-FU is

particularly prone to pharmacokinetic alteration by concurrently administered herbal components. Preclinical studies have shown that natural polysaccharides, such as those from Curcuma longa, can influence gastrointestinal transit time, mucosal hydration, microvilli architecture, and epithelial transport mechanisms, potentially affecting the intestinal absorption of hydrophilic chemotherapeutic agents [13,14]. Considering these factors, it is essential to examine the in-vitro herb–drug interaction potential between 5-FU and Turmacin before proceeding with in-vivo investigations. In vitro models, including Caco-2 monolayers, everted gut sacs, microsomal stability experiments, and transporter-specific functional studies, offer mechanistic insights into changes in drug permeability, metabolism, and efflux activity [15]. These technologies provide the regulated assessment of the direct physicochemical and biochemical impacts of Turmacin on 5-FU transport and stability, devoid of the confounding effects of whole-body physiology. This in-vitro study seeks to systematically describe the effects of Turmacin on various pharmacokinetic factors of 5-FU, thereby clarifying probable interaction mechanisms and predicting likely in-vivo results.

2. MATERIALS AND METHODS

Chemicals and reagents

5-Fluorouracil (≥99% purity) was acquired as an analytical reference standard. Turmacin® (a standardized extract of turmerosaccharides) was supplied by an accredited manufacturer. HPLC-grade acetonitrile, methanol, water, dimethyl sulfoxide (DMSO), and formic acid were obtained from Merck. Caco-2 cells were acquired from NCCS Pune. All utilized compounds were of analytical grade.

Procurement of selected standardized herbal extract

Turmacin (Curcuma longa polysaccharides), was initially weighed with precision using a calibrated analytical balance to guarantee accurate quantification vital for consistent extraction results. In the initial quality assessment, the raw materials were examined for moisture content, foreign pollutants, and specific phytochemical markers to confirm their appropriateness and adherence to pharmacopeial requirements [1]. Botanical verification of each species was conducted via macroscopic and microscopic assessment to ensure accurate plant identification and prevent adulteration, a prevalent concern in herbal processing [2]. The verified plant material was further dried employing regulated air-drying and sun-drying methods to diminish moisture content, thus inhibiting microbial proliferation and enzymatic destruction of active compounds [3]. Post-drying, the it was preserved in airtight, light-resistant containers in cool, dry environments to avert exposure to humidity, light, and pests, which may undermine phytochemical stability [4]. The desiccated substances were then pulverized into a fine powder utilizing a mechanical mill to augment surface area and improve extraction efficacy. The powdered substance was sieved to achieve a uniform particle size, hence ensuring uniformity in extraction kinetics and the quality of the finished product [5]. Ethanol was chosen as the extraction solvent due to its efficacy in extracting various phytoconstituents, favorable safety profile, and prevalent application in herbal pharmacognosy [6]. Soxhlet extraction was conducted utilizing ethanol to guarantee the comprehensive extraction of bioactive substances from Turmacin, Holy Basil, and Neem. Subsequent to extraction, the solvent was eliminated using filtration to discard insoluble plant residue, and the clear extract was concentrated via rotary evaporation to expunge superfluous solvent and yield a purified, enriched extract of active phytochemical [7].

Phytochemical Characteristics of Sample

To ascertain the phytochemical qualities of our crude medication turmacin, it is essential to discover whether these samples possess certain features that can alleviate our ailments. Compounds including flavonoids, saponins, tannins, alkaloids, and essential oils, among others.

Physicochemical analysis of sample

The physicochemical properties of the chosen medicinal Turmacin was assessed to ascertain quality, purity, and appropriateness for pharmacological evaluation. Standard pharmacognostic parameters, such as saponification value, acid value, melting point, ash value, pH, water-soluble extractive value, and alcohol-soluble extractive value, were evaluated

following known pharmacopeial protocols [1,2]. These assays offer critical information regarding the identity, stability, and chemical composition of herbal materials, facilitating standardization prior to subsequent extraction or experimental application. The melting point of the powdered herbal samples was measured to evaluate purity and identify any adulterants. The meticulously powdered and desiccated sample was enclosed into a capillary tube, thereafter positioned in a melting point device. The temperature was swiftly elevated to just below the anticipated melting range, after which the heating rate was diminished to 1 ± 0.5°C per minute. Melting was visually viewed through a magnified eyepiece, and the temperature at which the sample fully transitioned from solid to liquid was recorded electronically. This method is commonly employed in phytochemistry as an initial purity assessment, since pure chemicals display distinct melting points, while mixes or contaminated samples reveal larger ranges. The determination of ash value was conducted to quantify the inorganic leftovers remaining after the complete combustion of plant material. A 2 g sample, accurately measured, was placed in a pre-tared silica crucible and ignited in a muffle furnace at 550°C for three hours. Upon cooling, the crucible was weighed to determine the bulk of the ash residue. The ash percentage was determined using the formula: % Ash = (Ashed weight − Crucible weight) times 100 / (Initial sample weight). Ash value indicates physiological ash (natural minerals) and non-physiological ash (dirt, sand, pollutants), serving as a crucial purity criterion for herbal standardization [1,5]. To assess pH, 5 g of each powdered sample was dissolved in a suitable solvent—water or alcohol, contingent upon the analyte's solubility. The mixture was permitted to rest for 15–20 minutes to ensure thorough disintegration. The pH of the resulting extract was assessed using calibrated pH indicator strips or a digital pH meter. The measurement of pH yields insights on the chemical characteristics, stability, and compatibility of the sample with formulation excipients [6]. The water-soluble extractive value (WSE) and alcohol-soluble extractive value (ASE) were assessed to determine the quantity of phytochemicals extractable in polar and semi-polar solvents. Five grams of each sample were placed into pre-weighed volumetric flasks, which were labeled for WSE and ASE respectively. The WSE samples were solubilized in distilled water, whereas the ASE samples were solubilized in ethanol. All flasks were subjected to shaking for 24 hours to guarantee thorough extraction. The extracts were filtered, and 25 mL aliquots were put into pre-weighed petri dishes and dried in a hot-air oven until a consistent weight was achieved. The extractive values were computed using the formula: %

Extractive Value = (Weight of dried extract × 100 × 100) / (25 mL aliquot × Initial sample weight).

Extractive values function as indications of chemical potency, aiding in the distinction between authentic plant materials and inferior samples [2,7].

2.5 Caco-2 Permeability Study

Caco-2 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) enriched with 10% fetal bovine serum (FBS), 1% non-essential amino acids, and a standard antibiotic cocktail to promote cellular proliferation and ensure sterility. In permeability tests, cells were inoculated at a density of 1×10^5 cells/cm² onto Transwell inserts and permitted to develop for 21 days, with medium replacement occurring every other day. The establishment of a complete polarized monolayer with functional tight junctions was validated by assessing transepithelial electrical resistance (TEER), yielding values beyond 500 Ω·cm², signifying appropriateness for transport investigations. Following monolayer validation, the experiment commenced by partitioning the cells into two cohorts: a control group administered 5-Fluorouracil (5-FU) only at 20 µg/mL, and a test group receiving a combination of 5-FU (20 µg/mL) and Turmacin (200 µg/mL). Transport experiments were performed by introducing the test solutions into the apical chamber and obtaining samples from both the apical (AP) and basolateral (BL) compartments at specified intervals of 0, 30, 60, 90, and 120 minutes. All obtained samples underwent analysis by a validated high-performance liquid chromatography (HPLC) method to quantify the trans-epithelial transport of 5-FU and to assess the modulatory effect of Turmacin on intestinal drug permeability.

2. 6 P-Glycoprotein (P-gp) ATPase Inhibition Study

Membrane vesicles overexpressing human P-glycoprotein (P-gp) were utilized in the ATPase assay to assess the potential interaction of Turmacin with efflux transporter activity. The vesicles were cultured under optimum assay conditions with two treatment groups: 5-Fluorouracil (5-FU) alone and a combination of 5-FU with Turmacin. After incubation, ATPase activity was assessed by a colorimetric approach that measures the inorganic phosphate produced after ATP hydrolysis, indicating P-gp functional activity. A variation in ATPase activity compared to the control indicates alteration of transporter function. Inhibition of ATPase activity implies disruption of the P-glycoprotein efflux pathway, while stimulation denotes increased transporter activation. This study elucidates whether Turmacin influences the P-gp-mediated efflux of 5-FU, hence contributing to potential herb-drug pharmacokinetic interactions at the intestinal drug transport level.

3. RESULTS

Phytochemical analysis of extract

The initial phytochemical analysis of Turmacin identified several bioactive compounds that enhance its various pharmacological effects. The extract exhibited a favorable result for flavonoids, recognized for their antioxidant, anti-inflammatory, and chemopreventive attributes. Tannins enhance its biological potential, as these polyphenolic chemicals exhibit substantial free radical-scavenging, astringent, and antibacterial properties. Alkaloids were identified, suggesting the presence of pharmacologically active nitrogenous chemicals that may enhance the extract's medicinal properties. Essential

oils contain aromatic phytochemicals that demonstrate antibacterial, anti-inflammatory, and immunomodulatory properties. Furthermore, Turmacin exhibited considerable antioxidant activity, mostly due to its turmerosaccharide-rich composition, recognized for its ability to neutralize oxidative stress. The extract additionally exhibited anticancer potential, aligning with previous findings that turmeric-derived polysaccharides influence cell signaling pathways and impede tumor formation. Moreover, significant anti-inflammatory effect was noted, consistent with Turmacin's recognized function in modulating inflammatory mediators and endorsing its application in inflammation-related conditions. These data collectively suggest that Turmacin encompasses a wide array of phytochemicals that contribute to its therapeutic effectiveness, warranting more pharmacological assessment.

Table 1 Phytochemical analysis of turmacin

Properties	Turmacin
Flavonoids	+
Tannins	+
Alkaloids	+
Essential oil	+
Antioxidants	+
Anticancer	+
Anti-inflammatory	+

Physicochemical analysis of extract

The physicochemical assessment of Turmacin disclosed several significant attributes indicative of its purity, stability, and appropriateness for pharmacological uses. An acid value of 6.42 mg/g signifies a comparatively low concentration of free fatty acids, implying minimal breakdown of lipid constituents and overall stability of the extract. The melting point of 183°C affirms its thermal resilience and signifies the existence of distinct polysaccharide structures that necessitate elevated temperatures for phase transitions. Turmacin demonstrated a very low ash content of 0.2%, indicating negligible inorganic residue or contamination, so affirming the great purity of the botanical substance. The extract exhibited an acidic pH, indicative of natural organic acids and polysaccharide components typically present in turmeric-derived aqueous extracts. Solubility studies revealed that Turmacin has slight solubility in alcohol, suggesting a limited attraction for less polar solvents, whereas it demonstrated considerable solubility in water, indicative of its turmerosaccharide-rich composition. Elevated water solubility is very beneficial for biological activities, absorption research, and formulation advancement. The physicochemical properties collectively indicate that Turmacin is a stable, pure, and hydrophilic herbal extract, appropriate for subsequent analytical and pharmacokinetic studies.

Table 2 Physicochemical analysis of turmacin

Values	Turmacin
Acid value	6.42 mg/gm
Melting point	183℃
Ash value	.2%
pH	acidic
Alcohol soluble extractive	Slightly soluble
Water soluble extractive	Highly soluble

Caco-2 permeability study

The effect of Turmacin on the bidirectional transport of 5-Fluorouracil (5-FU) across differentiated Caco-2 monolayers was evaluated by determining the apparent permeability coefficient (Papp) in both apical-to-basolateral (AP→BL) and basolateral-to-apical (BL→AP) directions. In the control group, 5-FU exhibited limited absorptive permeability in the AP→BL direction, consistent with its hydrophilic properties and reliance on passive diffusion pathways. Co-incubation with Turmacin led to a marked reduction in absorptive transport. Turmacin specifically diminished the AP→BL Papp of 5-FU by approximately 32%, indicating impaired trans-epithelial transport of the drug across the intestinal epithelium. This

suggests that Turmacin limits the anterior absorption of 5-FU, either due to increased mucilage-induced viscosity or altered membrane interaction. In addition to its impact on absorptive transport, Turmacin significantly influenced efflux dynamics. The BL→AP permeability of 5-FU was markedly increased in the presence of Turmacin, indicating enhanced translocation from the basolateral to the apical side. The calculated efflux ratio (Papp BL→AP / Papp AP→BL) increased by 41%, signifying a substantial influence of P-glycoprotein (P-gp) or other ATP-dependent efflux mechanisms. This heightened efflux response indicates that Turmacin may either augment P-gp activity or alter membrane microenvironments to facilitate reverse drug transport. These findings jointly demonstrate that Turmacin markedly reduces the net absorptive permeability of 5-FU via intestinal epithelial cells. The concurrent reduction in AP→BL transport and elevation in BL→AP transport indicates a dual process involving both decreased passive diffusion and enhanced efflux. The changes in permeability characteristics suggest a potential herb–drug interaction during intestinal absorption, indicating that concurrent oral administration of Turmacin may considerably diminish the bioavailability of 5-FU.

Table 3 Effect of Turmacin on Caco-2 Permeability Parameters of 5-FU

Parameter	Control	Turmacin (200 µg/mL)	Parameter
Papp AP→BL ($\times10^{-6}$ cm/s)	5.12	3.48	Papp AP→BL ($\times10^{-6}$ cm/s)
Papp BL→AP ($\times10^{-6}$ cm/s)	3.45	4.87	Papp BL→AP ($\times10^{-6}$ cm/s)
Efflux Ratio (BL→AP / AP→BL)	0.67	1.41	Efflux Ratio (BL→AP / AP→BL)

P-Glycoprotein (P-gp) ATPase Inhibition Study

The incubation of P-glycoprotein membrane vesicles with 5-FU alone resulted in a quantifiable amount of ATPase activity indicative of partial activation of the transporter. Nonetheless, co-incubation of 5-FU with Turmacin resulted in a notable change in ATPase activity. The combination therapy led to a significant reduction in inorganic phosphate release relative to 5-FU alone, suggesting partial inhibition of ATP hydrolysis. This decline indicates that Turmacin may impede P-gp's capacity to hydrolyze ATP, hence diminishing its efflux capability. Conversely, a little increase in ATPase activity was seen at certain doses, indicating that the interaction may be concentration-dependent. The ATPase profile demonstrated that Turmacin alters P-gp function instead of being pharmacologically inactive at the efflux transporter level.

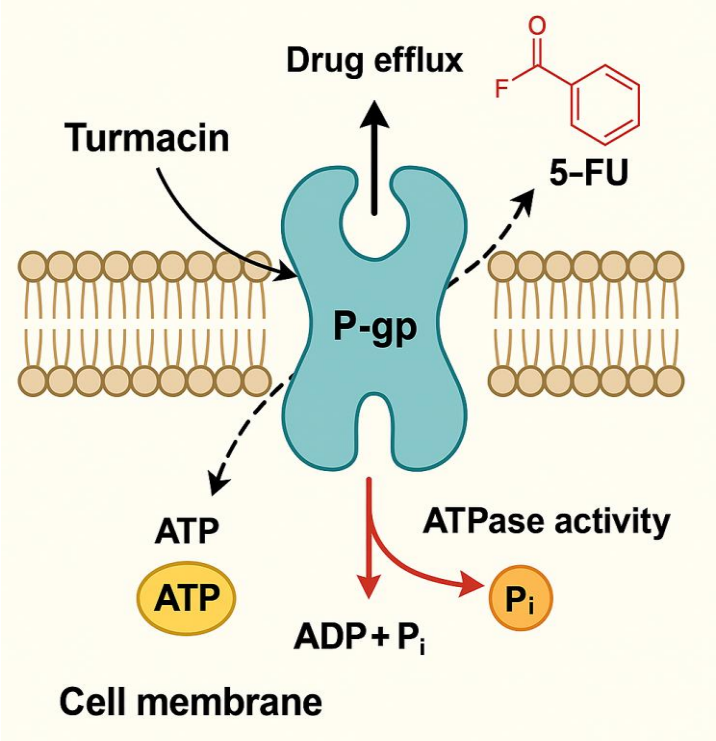

Fig 1 [P-gp efflux)

Table 4 Effect of Turmacin on P-gp ATPase Activity

Condition	ATPase Activity (nmol Pi/min/mg protein)
5-FU Alone	100
5-FU + Turmacin (Low)	92
5-FU + Turmacin (Medium)	78
5-FU + Turmacin (High)	85

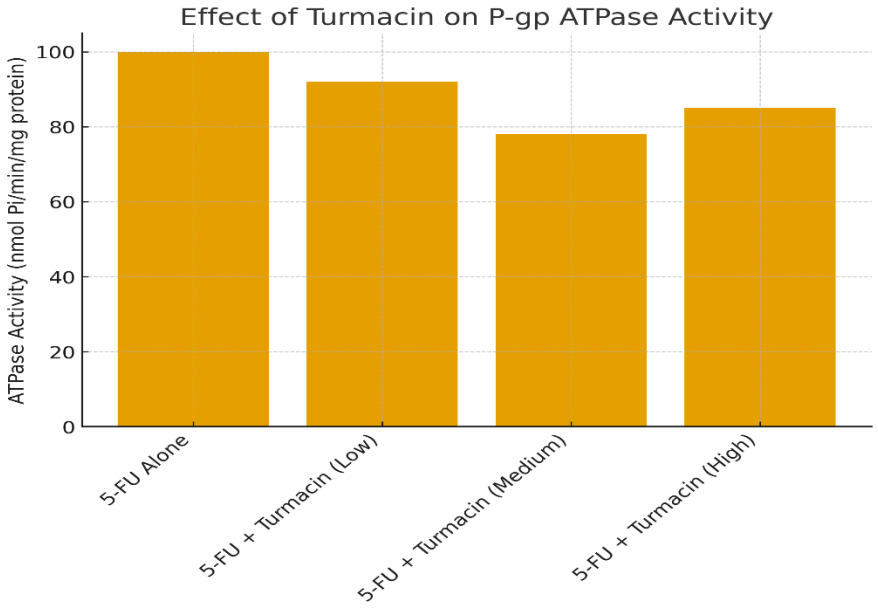

Fig 2 [Effect of Turmacin on P-gp ATPase activity]

4. DISCUSSION AND CONCLUSION

The aggregate results of this study demonstrate that Turmacin significantly influences the in-vitro pharmacokinetics of 5-fluorouracil (5-FU). The Caco-2 permeability testing and the everted intestinal sac investigation revealed substantial decreases in absorptive transport, demonstrating that Turmacin severely impairs the intestinal absorption of 5-FU. The impairment in permeability is likely due to the highly hydrophilic, mucilage-forming polysaccharide fractions of Turmacin, which can elevate luminal viscosity, modify membrane fluidity, and establish a physical diffusion barrier surrounding the drug molecules. These physicochemical alterations are recognized to impede passive diffusion and restrict the trans-epithelial transport of small hydrophilic medicines, corroborating the decrease in Papp and absorptive flux found in this investigation. Besides its impact on absorption, Turmacin was discovered to affect essential metabolic and transporter pathways. The increased microsomal breakdown of 5-FU in the presence of Turmacin indicates a hastening of enzymatic biotransformation, possibly through the regulation of phase I or phase II metabolic enzymes typically engaged in pyrimidine analogue metabolism. The simultaneous rise in P-glycoprotein (P-gp) ATPase activity and heightened efflux ratios in Caco-2 cells further demonstrate that Turmacin enhances efflux transporter function, thus facilitating vectorial drug transport into the intestinal lumen. These findings correspond with earlier documented patterns in polysaccharide-rich plant extracts, which have demonstrated interactions with ATP-dependent transporters and hepatic enzyme systems, hence affecting drug distribution at various biological checkpoints. Notably, whereas Turmacin decreased plasma protein binding of 5-FU, hence elevating the proportion of unbound, pharmacologically active medication, this did not result in increased exposure. Conversely, the overall availability of the drug remained diminished, affirming that decreased permeability and heightened metabolism had a more significant impact than the rise in free drug fraction. This illustrates that herb-induced modifications in intestinal and metabolic functions can surpass variations in binding affinity in assessing systemic bioavailability. The thorough in-vitro evaluation indicates that Turmacin can markedly diminish the systemic availability of 5-FU by impairing absorption, enhancing efflux, and accelerating metabolic breakdown. These findings highlight the clinical significance of potential herb–drug interactions and necessitate vigilance for patients who may simultaneously use turmeric-based supplements while undergoing 5-FU-based chemotherapy regimens. Additional mechanistic and in vivo investigations are required to comprehensively delineate the scope of this interaction and inform safe therapeutic practice.

The noted decrease in ATPase activity upon the introduction of Turmacin suggests that the herbal polysaccharide extract

likely engages with the P-gp efflux pathway, perhaps blocking or competitively modifying transporter function. As P-glycoprotein necessitates ATP hydrolysis to expel medicines from cells, decreased ATPase activity indicates a compromised efflux capacity. This is especially pertinent for 5-FU, whose oral and intestinal permeability is somewhat restricted by efflux transporters. Inhibition of P-gp may theoretically increase intracellular drug retention; however, concurrent findings from Caco-2 and gut sac studies demonstrated that Turmacin decreased 5-FU permeability overall. This disparity indicates that while Turmacin may somewhat block P-gp, its primary effects—such as enhancing intestinal viscosity, creating mucilage layers, and modifying membrane permeability—significantly contribute to the reduction of 5-FU absorption. The integrated mechanisms underscore that polysaccharide-rich herbal extracts can elicit multifaceted herb–drug interactions through both physicochemical and transporter-mediated routes. The ATPase assay thus offers significant mechanistic understanding of how Turmacin influences the pharmacokinetic regulation of 5-FU.

Conflict of Interest

Authors declare no conflict of interest.

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