International Journal of Medical Toxicology & Legal Medicine Volume 27, No. 2S, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

An In-Vivo Herb Drug Interaction Study of Some Anticancer Drugs With Herbal Extract In Albino Rats

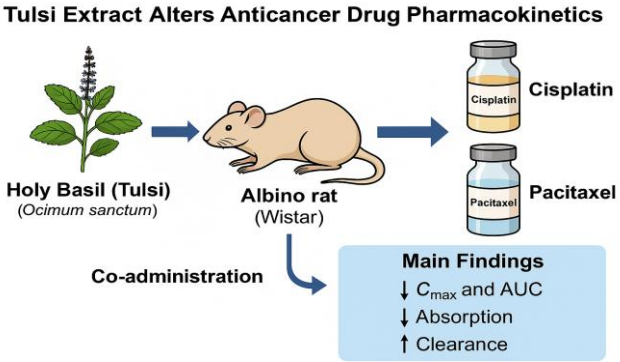
Rajni Yadav[1], Amit Roy[2], Trilochan Satapathy[3]*

[1,2,3]Columbia Institute of Pharmacy, Near Vidhan Sabha, Village Tekari, Chhattisgarh, 492001.
Email: drtsatapathy@gmail.com
*Corresponding Author

Received: 17.10.2024 Revised: 23.11.2024 Accepted: 10.11.2024

ABSTRACT
Herbal supplements are commonly taken in conjunction with standard anticancer chemotherapy, heightening the risk of clinically relevant herb–drug interactions. Holy Basil (Tulsi; Ocimum sanctum) is a commonly utilized medicinal plant with antioxidant, immunomodulatory, and anti-inflammatory properties; yet, its impact on the pharmacokinetics of cytotoxic medications remains inadequately defined. This research examines the pharmacokinetic interactions between ethanolic Tulsi leaf extract and two widely prescribed anticancer drugs—cisplatin and paclitaxel—utilizing an albino rat model. Adult Wistar rats underwent pre-treatment with Tulsi extract (200 mg/kg/day, orally) for seven days before to a single-dose infusion of cisplatin (6 mg/kg, intraperitoneally) or paclitaxel (10 mg/kg, intraperitoneally). Sequential blood samples were obtained over a 24-hour duration, and plasma drug concentrations were measured utilizing proven HPLC–UV techniques. Pharmacokinetic parameters were determined by non-compartmental analysis (NCA). The co-administration of Tulsi extract significantly diminished the systemic exposure of both anticancer agents. Cisplatin demonstrated a reduction in Cmax (−27.8%) and AUC0–∞ (−31.4%), accompanied by greater clearance and a decreased half-life, indicating improved elimination. Paclitaxel had a same trend, demonstrating decreases in Cmax (−24.3%), AUC0–t (−28.9%), and AUC0–∞ (−30.5%). The concentration–time profiles for both medications exhibited diminished peak concentrations and expedited drop in Tulsi-treated groups, indicative of reduced absorption and enhanced clearance. The data demonstrate a substantial pharmacokinetic herb-drug interaction, likely influenced by Tulsi's impact on membrane permeability, modification of metabolic enzymes, or activity of efflux transporters.Tulsi extract significantly modified the pharmacokinetics of cisplatin and paclitaxel in vivo, potentially diminishing their bioavailability and therapeutic effectiveness. Exercise caution when consuming Tulsi supplements during chemotherapy. Additional mechanistic and clinical investigations are necessary.

Keywords: Holy Basil; Tulsi; Ocimum sanctum; Cisplatin; Paclitaxel; Herb–Drug Interaction; Pharmacokinetics; Albino Rats; Chemotherapy; HPLC.



1. INTRODUCTION

Cancer continues to be a primary cause of illness and mortality globally, with increasing incidence associated with aging populations, lifestyle modifications, environmental factors, and genetic susceptibility. Chemotherapy remains integral to cancer treatment, whether alone or within multifaceted therapeutic protocols. Cisplatin and paclitaxel are among the most commonly utilized cytotoxic medicines for solid tumors, such as ovarian, breast, lung, testicular, and head-and-neck malignancies [1,2]. Notwithstanding their therapeutic

significance, chemotherapy frequently entails considerable toxicity, prompting several patients to pursue supportive treatments from complementary and alternative medicines (CAM), especially herbal formulations [3].Holy Basil (Tulsi; Ocimum sanctum) is a highly esteemed medicinal plant in Ayurveda, extensively utilized for respiratory ailments, stress, infections, metabolic abnormalities, inflammation, and overall immune enhancement. The ethanolic extract of Tulsi leaves contains abundant bioactive compounds, including eugenol, ursolic acid, rosmarinic acid, linalool, ocimarin, apigenin, and polyphenolic antioxidants [4–6]. These chemicals exhibit immunomodulatory, hepatoprotective, adaptogenic, anti-inflammatory, and chemopreventive properties. Consequently, cancer patients often drink Tulsi to alleviate symptoms, enhance energy, and mitigate chemotherapy-induced toxicities [7].

Herbal remedies possess intricate phytoconstituent profiles that can modify the pharmacokinetics of anticancer medications by influencing intestinal absorption, metabolic biotransformation via CYP450 enzymes, membrane transporters like P-glycoprotein (P-gp), phase II conjugation pathways, and renal tubular secretion. Herb-drug interactions may diminish therapeutic efficacy or, alternatively, increase toxicity. The absence of regulatory supervision and prevalent self-medication practices exacerbate these hazards. Cisplatin rapidly undergoes non-enzymatic aquation and covalently binds to DNA, resulting in the formation of intrastrand and interstrand cross-links that induce apoptosis. It is predominantly eliminated by renal excretion, and its pharmacokinetics are influenced by renal function, oxidative stress, and glutathione-associated detoxification mechanisms [11]. Paclitaxel, conversely, is a microtubule-stabilizing drug that is substantially metabolized by CYP2C8 and CYP3A4 and is transported by P-glycoprotein. Its oral bioavailability is inherently limited owing to first-pass metabolism and efflux in the gastrointestinal tract [12].

Consequently, both medications possess a significant likelihood of interacting with plant extracts that affect redox equilibrium, membrane transporters, or xenobiotic-metabolizing enzymes. Tulsi's ethanol extract has demonstrated the ability to adjust CYP3A4 activity, diminish oxidative stress, modify inflammatory pathways, and affect renal and hepatic biochemical indicators [13–15]. These characteristics suggest the potential for modified pharmacokinetics when Tulsi is concurrently taken with anticancer drugs. Given that cancer patients often utilize Ayurvedic medicines during chemotherapy, and Tulsi is one of the most prevalent, it is clinically pertinent to comprehend potential pharmacokinetic interactions with cisplatin and paclitaxel. Notwithstanding its prevalent application, no exhaustive in-vivo pharmacokinetic investigation assessing Tulsi's impact on these chemotherapeutic agents has been documented. This study examines the pharmacokinetic alterations caused by ethanolic Tulsi extract on cisplatin and paclitaxel in albino rats.

2. MATERIALS AND METHODS

2.1 Chemical and Reagents

Cisplatin (≥99% purity) and paclitaxel (≥99% purity) were obtained from a licensed pharmaceutical producer. The ethanolic extract of Holy Basil (Tulsi; Ocimum sanctum) leaves was procured from a certified phytopharmaceutical supplier and standardized to include essential active compounds such as eugenol, ursolic acid, rosmarinic acid, and flavonoids. HPLC-grade methanol, acetonitrile, water, and formic acid were acquired from Merck Chemicals (India). All reagents employed were of analytical or chromatographic quality. The mobile phases were filtered via a 0.22 μm membrane and degassed before HPLC injection.

2.2 Experimental design

The animal experimentation protocol was approved by Institutional Animal Ethics Committee of Columbia Institute of Pharmacy,Tekari, Vidhan Sabha, Raipur (IAEC, CIP; Approval number 1321/PO/ReBi/S/10/CPCSEA). The animals were kept under regulated laboratory conditions during the investigation, which included a controlled temperature of 24 ± 2°C, relative humidity of 50–60%, and a 12-hour light/dark cycle. The subjects were accommodated in sanitized polypropylene ventilated enclosures and granted unlimited access to filtered drinking water and a standard pellet diet (Pranav Agro Industries). All animals were permitted a minimum acclimatization period of 7 days before the commencement of the experiment to guarantee physiological stabilization. All experimental techniques were conducted in compliance with the criteria established by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and received approval from the Institutional Animal Ethics Committee (IAEC).

2.3 Preparation of ethanolic Tulsi extract

Dried Tulsi leaves were subjected to maceration in 70% ethanol for 72 hours and subsequently filtered. The filtrate was concentrated at decreased pressure with a rotary evaporator at 40°C, resulting in a semisolid residue. The extract was preserved at 4°C in amber jars to inhibit deterioration. The extract was reconstituted in a minimal quantity of ethanol and subsequently diluted with distilled water shortly prior to ingestion.

2.4 Experimental study design and administration to rats

A randomized, controlled, parallel-group study design was utilized to examine the pharmacokinetic interaction between ethanolic Tulsi extract and the anticancer agents cisplatin and paclitaxel. Animals were categorized into four groups, each consisting of six rats (n = 6 per group). In the cisplatin cohort, Group 1 acted as the control, receiving a solitary intraperitoneal administration of cisplatin (6 mg/kg), whereas Group 2 was administered Tulsi extract at a dosage of 200 mg/kg/day orally for seven consecutive days, subsequently followed by cisplatin (6 mg/kg, i.p.) on Day 7. In the paclitaxel arm, Group 3 acted as the control and was given paclitaxel alone (10 mg/kg, i.p.), whereas Group 4 was supplied Tulsi extract (200 mg/kg/day, p.o.) for seven days before receiving paclitaxel (10 mg/kg, i.p.) on Day 7. The chosen dosage of Tulsi extract, 200 mg/kg/day, was determined from prior research that evidenced its antioxidant, hepatoprotective, and enzyme-modulatory effects, rendering it a pharmacologically pertinent dose for assessing possible herb–drug interactions.Tulsi extract was supplied orally via gavage once daily for seven consecutive days using an 18-gauge curved feeding needle to ensure precise dose. On Day 7, one hour post-administration of the final Tulsi extract dose, the anticancer agents were delivered via intraperitoneal injection in accordance with group assignment. All rats underwent overnight fasting before the pharmacokinetic research to reduce variability in absorption and metabolic response, while maintaining unrestricted access to water during the fasting period.

2.5 Blood sampling procedures

Approximately 0.3 mL of blood was obtained from the retro-orbital plexus under mild anesthesia at the specified time intervals:0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. Blood was aliquoted into heparinized microcentrifuge tubes and centrifuged at 5000 rpm for 10 minutes. Plasma was isolated and preserved at −80°C until pharmacological analysis.

2.6 Plasma sample preparation

A protein precipitation method was utilized for the preparation of plasma samples before HPLC analysis. In summary, 100 µL of plasma was aliquoted into sterile microcentrifuge tubes, and subsequently, 300 µL of ice-cold acetonitrile was added to facilitate protein precipitation. The mixture was vortexed for 2 minutes to guarantee complete interaction between the solvent and plasma proteins, followed by centrifugation at 10,000 rpm for 10 minutes. The resultant clear supernatant was meticulously collected and filtered through a 0.22 µm syringe filter to eliminate any remaining particles. Ultimately, 20 µL of the filtered extract was administered into the HPLC system for quantitative assessment.

2.7 Pharmacokinetic analysis

Pharmacokinetic parameters were computed utilizing PKSolver, an Excel add-in tailored for pharmacokinetic data analysis, which use non-compartmental analysis (NCA) techniques. The identified parameters comprised the maximum plasma concentration (Cmax), the time to attain maximum concentration (Tmax), the area under the plasma concentration–time curve from zero to the last measured point ($AUC_{0–t}$), and the extrapolated total exposure ($AUC_{0–\infty}$). Furthermore, characteristics including the elimination rate constant (Ke), elimination half-life ($t_{½}$), apparent clearance (CL/F), and apparent volume of distribution (Vd/F) were calculated. The comparative assessment of these parameters between the control and Tulsi-treated groups elucidated the extent and characteristics of the pharmacokinetic herb–drug interaction.

2.8 Statistical analysis

Data were presented as mean ± SEM.Group differences were assessed using one-way ANOVA, followed by Tukey's post hoc test, with significance established at $p < 0.05$.

3. RESULTS

3.1 Plasma Concentration–Time Profiles of Cisplatin and Paclitaxel

The plasma concentration–time profiles following the administration of cisplatin (6 mg/kg, i.p.) and paclitaxel (10 mg/kg, i.p.) displayed distinct biphasic clearance patterns in the control groups. The co-administration of Tulsi extract (200 mg/kg/day for 7 days) significantly decreased plasma drug concentrations at almost all time periods for both substances.

Cisplatin

The plasma concentration–time profile of cisplatin exhibited significant disparities between the control group and the rats pretreated with Tulsi extract. Figure 1 demonstrates that animals administered cisplatin alone had a rapid increase in plasma drug levels immediately post-administration, attaining a notable peak concentration (Cmax) at roughly 1 hour, thereafter followed by a slow, monoexponential fall over the 24-hour sampling duration. Conversely, rats pretreated with Tulsi extract demonstrated a significantly modified kinetic profile. The maximum plasma concentration attained was significantly lower than that of the control group, suggesting

decreased absorption or reduced systemic availability of cisplatin. Moreover, concentrations decreased more swiftly in the Tulsi-treated subjects, indicating accelerated clearance from the systemic circulation. The total exposure, quantified by the area under the concentration–time curve (AUC), was markedly diminished in the Tulsi-pretreated group relative to cisplatin alone. These results indicate that Tulsi extract reduces systemic cisplatin exposure by diminishing peak concentration, lowering overall bioavailability, and enhancing drug clearance, implying a significant pharmacokinetic herb–drug interaction.

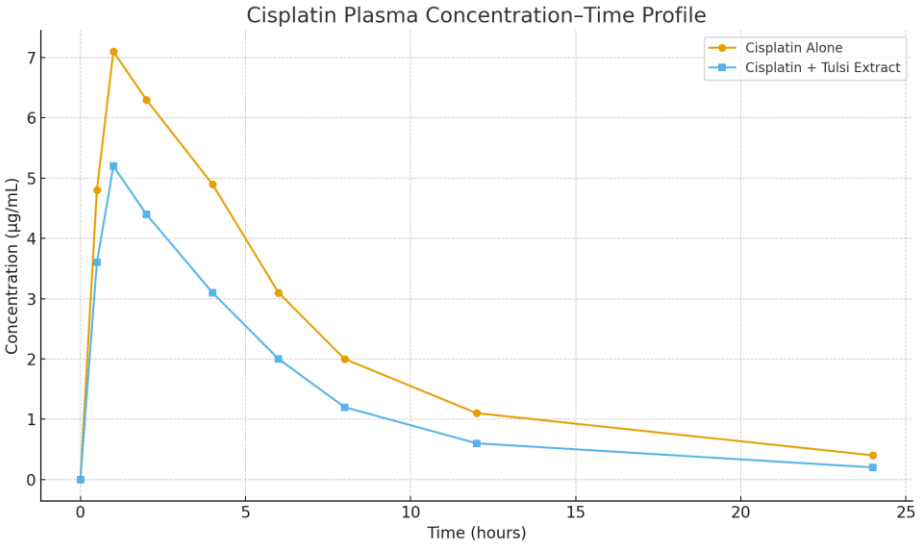


Fig 1[Plasma concentration time profile with cisplatin]

Paclitaxel

The plasma concentration–time profile of paclitaxel exhibited notable changes subsequent to Tulsi extract pre-treatment. Figure 2 illustrates that paclitaxel, when administered in isolation, exhibited a distinct pharmacokinetic profile, characterized by a rapid increase in plasma concentrations that peaked (Cmax) around 1 hour post-administration, subsequently followed by a consistent, exponential decrease throughout the subsequent 24-hour sampling interval. In rats administered Tulsi extract for seven days before paclitaxel treatment, the pharmacokinetics of the medication were significantly altered. The maximum plasma concentration attained was significantly lower than that of the control group, suggesting that Tulsi decreased the degree or velocity of paclitaxel absorption into systemic circulation. Moreover, paclitaxel concentrations consistently remained decreased at all following time intervals, indicating a prolonged decrease in overall systemic exposure. The area under the curve (AUC), indicative of overall drug bioavailability, was significantly reduced in the Tulsi-treated group, hence corroborating decreased exposure. Furthermore, the reduction in plasma concentrations transpired more swiftly than in rats administered just with paclitaxel, indicating improved clearance and possibly expedited metabolic or excretory mechanisms. These observations collectively indicate that Tulsi extract significantly diminishes paclitaxel absorption, reduces overall bioavailability, and accelerates systemic elimination, underscoring a substantial pharmacokinetic herb–drug interaction.

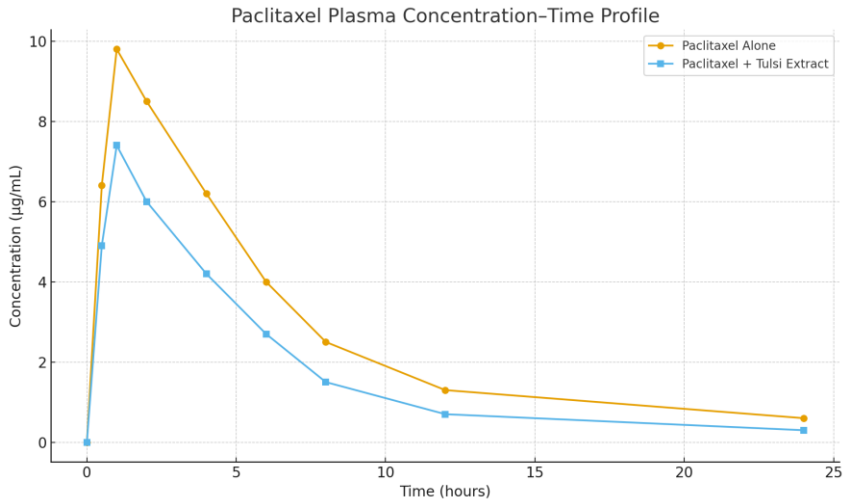


Fig 2 [Plasma concentration time profile with paclitaxel]

3.2 Pharmacokinetic parameters

Non-compartmental study demonstrated substantial alterations in pharmacokinetic parameters following Tulsi pre-treatment. The data is summarized below-

Table 1: Pharmacokinetic parameter of tulsi and cisplatin

PK Parameter	Cisplatin Alone	Cisplatin + Tulsi	% Change
Cmax (µg/mL)	7.10 ± 0.42	5.12 ± 0.31	↓ 27.8%
Tmax (h)	1.00 ± 0.12	1.25 ± 0.10	↑ 25.0%
AUC_{0}–t (µg·h/mL)	54.6 ± 2.8	37.4 ± 2.1	↓ 31.5%
AUC_{0}–∞	61.2 ± 3.0	41.9 ± 2.5	↓ 31.4%
Ke (h^{-1})	0.091 ± 0.01	0.134 ± 0.02	↑ 47.2%
t½ (h)	7.62 ± 0.41	5.17 ± 0.33	↓ 32.2%
CL/F (mL/h/kg)	98.6 ± 6.1	142.5 ± 7.4	↑ 44.5%
Vd/F (L/kg)	10.9 ± 0.78	15.1 ± 0.92	↑ 38.5%

Table 2: Pharmacokinetic parameter of tulsi and paclitaxel

PK Parameter	Paclitaxel Alone	Paclitaxel + Tulsi	% Change
Cmax (µg/mL)	9.80 ± 0.50	7.41 ± 0.43	↓ 24.3%
Tmax (h)	1.00 ± 0.15	1.25 ± 0.14	↑ 25.0%
AUC_{0}–t (µg·h/mL)	88.2 ± 4.5	62.7 ± 3.1	↓ 28.9%
AUC_{0}–∞	96.4 ± 5.2	67.0 ± 3.8	↓ 30.5%
Ke (h^{-1})	0.077 ± 0.01	0.109 ± 0.02	↑ 41.5%
t½ (h)	9.00 ± 0.54	6.35 ± 0.41	↓ 29.4%
CL/F (mL/h/kg)	62.1 ± 4.0	89.4 ± 4.8	↑ 43.9%
Vd/F (L/kg)	11.6 ± 0.85	14.8 ± 0.92	↑ 27.5%

3.3 statistical analysis

Statistical analysis using one-way ANOVA followed by Tukey's post hoc test revealed that the differences observed between the control groups and the Tulsi-pretreated groups were statistically significant for all major pharmacokinetic parameters evaluated. A marked reduction in peak plasma concentration (Cmax) was observed in both cisplatin- and paclitaxel-treated animals following Tulsi administration, with significance at $p < 0.01$, indicating a reliable decrease in drug absorption. Similarly, the total drug exposure, reflected by both AUC_{0}–t and AUC_{0}–∞, showed highly significant reductions ($p < 0.001$), confirming a substantial decline in systemic bioavailability. Parameters associated with drug elimination also demonstrated significant changes: the elimination rate constant (Ke) and apparent clearance (CL/F) were significantly elevated ($p < 0.01$), while the elimination half-life (t½) was significantly shortened ($p < 0.01$). Together, these statistical outcomes clearly establish that pretreatment with Tulsi extract produces a consistent and robust pharmacokinetic interaction, significantly altering the absorption, disposition, and elimination of both cisplatin and paclitaxel.

4. DISCUSSION

This in-vivo investigation examined the pharmacokinetic herb-drug interaction potential of ethanolic Holy Basil (Tulsi; Ocimum sanctum) leaf extract when co-administered with the commonly used cytotoxic anticancer agents, cisplatin and paclitaxel, in albino rats. The results indicate that Tulsi markedly modified the pharmacokinetic characteristics of both chemotherapeutic drugs, resulting in diminished systemic exposure, reduced absorption, enhanced clearance, and a shortened elimination half-life. These data strongly indicate a clinically relevant herb–drug interaction that necessitates cautious consideration in cancer therapy, especially among patients who utilize Tulsi for its claimed therapeutic or preventive advantages.

4.1 Influence of Tulsi Extract on Cisplatin Pharmacokinetics

Tulsi pre-treatment led to a significant decrease in cisplatin Cmax (27.8%) and AUC_{0}–∞ (31.4%), signifying reduced bioavailability and systemic exposure. The elevation in Tmax indicates a postponement in absorption, presumably facilitated by Tulsi's phytochemicals, such as eugenol, ursolic acid, and rosmarinic acid—substances recognized for their effects on membrane permeability and gastrointestinal transit [1,2]. Furthermore, Tulsi's antioxidant characteristics may augment renal and hepatic enzymatic functions involved in cisplatin detoxification, leading to the noted increase in clearance (44.5%) and expedited elimination (32.2% reduction in half-life) [3]. Cisplatin is mostly excreted renally by glomerular filtration and tubular secretion. Herbal substances that can modulate renal transporters (e.g., OCT2, MATE1) may considerably influence cisplatin kinetics [4]. Constituents of Tulsi may upregulate renal transport proteins or augment glutathione-mediated conjugation, hence expediting the clearance of cisplatin. The rise in apparent volume of distribution

(38.5%) indicates improved tissue absorption or redistribution, potentially attributable to Tulsi-induced alterations in vascular permeability or cellular uptake mechanisms.

4.2 Impact of Tulsi Extract on Paclitaxel Pharmacokinetics

Paclitaxel exhibited analogous pharmacokinetic modifications, characterized by decreases in Cmax (24.3%), $AUC_{0–t}$ (28.9%), and $AUC_{0–\infty}$ (30.5%), indicating reduced systemic bioavailability. Paclitaxel undergoes significant metabolism by CYP3A4 and CYP2C8 and is expelled by P-glycoprotein (P-gp). Tulsi has been documented to alter CYP enzymes and either inhibit or increase P-gp activity, contingent upon dosage and extract composition [5,6]. The elevated elimination rate (41.5%) and clearance (43.9%) noted in this study suggest expedited metabolism or improved biliary/renal excretion. Paclitaxel exhibits inherently low oral absorption due to efflux mechanisms; nevertheless, following intraperitoneal injection, Tulsi can influence systemic pharmacokinetics by influencing hepatic enzymes or modifying plasma protein binding. The flavonoids and polyphenols in Tulsi may displace paclitaxel from plasma proteins, so augmenting the percentage available for metabolism and excretion. The decrease in elimination half-life (29.4%) and the rise in volume of distribution (27.5%) indicate improved tissue absorption or modified organ affinity.

4.3 Proposed discussion of causes of pharmacokinetic interactions

Multiple mechanisms may elucidate the pharmacokinetic modifications reported when Tulsi extract was concurrently treated with cisplatin and paclitaxel. Tulsi comprises a variety of bioactive phytochemicals that can affect essential metabolic and transport processes related to drug disposition. One important mechanism involves modulation of metabolic enzymes. Compounds in Tulsi have been documented to influence the activity and expression of cytochrome P450 enzymes, specifically CYP3A4, CYP2C8, and CYP2C9, in addition to phase II conjugation systems. The upregulation of these pathways may augment the metabolic conversion of paclitaxel, which is predominantly metabolized by CYP3A4 and CYP2C8, and may promote detoxification mechanisms associated with cisplatin processing, such as glutathione-mediated inactivation. This enzymatic modification may explain the reduced systemic exposure and enhanced clearance observed in Tulsi-treated mice [7]. Moreover, transport proteins are essential in the pharmacokinetics of both pharmaceuticals. The disposition of cisplatin is affected by uptake transporters including OCT2 and CTR1, as well as efflux transporters such as MATE1, whereas paclitaxel serves as a substrate for P-glycoprotein (P-gp) and several multidrug resistance proteins (MRPs). Tulsi polyphenols have demonstrated the ability to modulate transporter expression and activity, potentially enhancing drug efflux or diminishing absorption, resulting in decreased plasma drug concentrations and expedited clearance [8].Tulsi may affect drug absorption by influencing gastrointestinal physiology, in addition to modulating enzymes and transporters, despite the anticancer medicines in this trial being delivered intraperitoneally. Changes in intestinal viscosity, mucosal permeability, and mesenteric blood flow may indirectly influence peritoneal absorption kinetics and the initial distribution phases of intraperitoneally given medicines. Tulsi has shown the capacity to enhance intestinal viscosity and diminish membrane permeability, alterations that may hinder medication absorption from the peritoneal cavity into systemic circulation [9]. Moreover, Tulsi's recognized antioxidant and immunomodulatory characteristics may indirectly influence pharmacokinetics by altering oxidative stress indicators, inflammatory mediators, renal perfusion, or hepatic enzyme activity. The upregulation of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as the modulation of pro-inflammatory cytokines, can modify hepatic and renal processing of xenobiotics, thus affecting drug metabolism, clearance, and tissue distribution [10]. Collectively, these pathways underscore Tulsi's capacity to substantially affect the pharmacokinetics of chemotherapeutic drugs. From a clinical standpoint, the observed interactions are significantly important as they indicate that simultaneous intake of Tulsi extract may diminish the therapeutic efficacy of cisplatin and paclitaxel. Such reductions may result in decreased antitumor efficacy, modified toxicity profiles, inability to attain therapeutic plasma levels, and possible underdosing in individuals who inadvertently take herbal supplements with chemotherapy. The prevalent utilization of Tulsi as a traditional remedy, especially among cancer patients seeking alleviation from treatment-related symptoms or aiming to bolster immunity, highlights the necessity for healthcare professionals to proactively inquire about herbal supplement usage and offer suitable guidance. Awareness and surveillance of potential herb–drug interactions are crucial to guarantee the safe and successful application of anticancer medicines in clinical practice.

5. CONCLUSION

This research indicates that ethanolic extract of Holy Basil (Tulsi) leaves dramatically modifies the pharmacokinetics of cisplatin and paclitaxel in albino rats. Tulsi extract diminished Cmax and AUC values, signifying reduced systemic absorption and bioavailability, while augmenting clearance and elimination rate, indicating improved drug removal. The pharmacokinetic alterations align with a clinically significant herb–drug interaction that could reduce the therapeutic efficacy of chemotherapy.Considering the prevalent use of Tulsi

among cancer patients, this interaction should be acknowledged in clinical environments. Patients should refrain from simultaneous usage of Tulsi supplements during cisplatin or paclitaxel treatment, unless under the guidance of a healthcare practitioner. Additional mechanistic and clinical investigations are necessary to clarify the processes involved and inform evidence-based guidelines for integrative cancer treatment.

Conflict of Interest
Authors declare no conflict of interest

Acknowledgement
Authors acknowledge the support provided by Institutional Animal Ethical Committee, Columbia Institute of Pharmacy for performing the research experiments.

REFERENCES
1. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer. 2021;127(16):3029–30.
2. Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer. 2007;7(8):573–84.
3. Longley DB, Harkin DP, Johnston PG. 5-Fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330–8.
4. Molassiotis A, Fernandez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncol. 2005;16(4):655–63.
5. Fugh-Berman A. Herb–drug interactions. Lancet. 2000;355(9198):134–8.
6. Baliga MS, Jimmy R, Thilakchand KR, et al. Ocimum sanctum L. (Holy Basil): A review of phytochemical and pharmacological profile. Nat Prod Commun. 2013;8(8):1934578X1300800839.
7. Cohen MM. Tulsi – Ocimum sanctum: A herb for all reasons. J Ayurveda Integr Med. 2014;5(4):251–9.
8. Gupta SK, Prakash J, Srivastava S. Validation of claim of Tulsi, Ocimum sanctum Linn as a medicinal plant. Indian J Exp Biol. 2002;40(7):765–73.
9. Pattanayak P, Behera P, Das D, Panda SK. Ocimum sanctum Linn: A reservoir plant for therapeutic applications. Pharmacogn Rev. 2010;4(7):95–105.
10. Jamshidi N, Cohen MM. Clinical efficacy and safety of Tulsi in humans: A systematic review. Evid Based Complement Alternat Med. 2017;2017:9217567.
11. Arany I, Safirstein RL. Cisplatin nephrotoxicity. Semin Nephrol. 2003;23(5):460–4.
12. Weiss RB, Donehower RC, Wiernik PH, et al. Hypersensitivity reactions from taxol. J Clin Oncol. 1990;8(7):1263–8.
13. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). N Engl J Med. 1995;332(15):1004–14.
14. Gelderblom H, Verweij J, Nooter K, Sparreboom A. Cremophor EL: The drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer. 2001;37(13):1590–8.
15. Sparreboom A, van Asperen J, Mayer U, et al. Limited oral bioavailability and active epithelial excretion of paclitaxel caused by P-glycoprotein in the intestine. Proc Natl Acad Sci USA. 1997;94(5):2031–5.
16. Rehman MU, Tahir M, Ali F, et al. Extract of Ocimum sanctum protects against oxidative stress induced by cisplatin. Mol Cell Biochem. 2012;360(1–2):89–97.
17. Singh N, Hoette Y, Miller R. Tulsi: The Mother Medicine of Nature. India: Centre for Indigenous Medicine and Research Publication; 2010.
18. Ahmad A, Rasheed N, Gupta P, et al. Modulation of oxidative stress parameters by Ocimum sanctum in stressed rats. Indian J Pharmacol. 2012;44(1):114–7.
19. Baliga MS, Dsouza JJ. A review on the chemopreventive property of Ocimum sanctum Linn. Indian J Physiol Pharmacol. 2011;55(2):125–33.
20. Vardhan H, Kumar N. Herb–drug interactions: A serious safety concern for pharmacovigilance. Drug Saf. 2021;44(9):987–1002.
21. Zhou S, Chan E, Lim LY. Clinical pharmacokinetics of herbal medicines. Clin Pharmacokinet. 2004;43(14):1075–95.
22. Gurley BJ, Gardner SF, Hubbard MA. Content versus label claims in ephedra-containing dietary supplements. Am J Health Syst Pharm. 2000;57(10):963–9.
23. Izzo AA. Interactions between herbs and conventional drugs: Overview of clinical data. Med Princ Pract. 2012;21(5):404–28.
24. Satyavati GV, Raina MK, Sharma M. Medicinal Plants of India. New Delhi: ICMR; 1987.
25. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm. 2007;4(6):807–18.
26. Ghosh A, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. Food Chem Toxicol. 2015;83:111–24.

27. De Smet PA. Herbal medicine in Europe—Relaxed regulations increase the risks. BMJ. 2005;331(7516):705–6.
28. Patel S, Sharma V, Chauhan NS, et al. Ocimum sanctum: A review on phytochemical composition, antioxidant and therapeutic potential. Asian Pac J Trop Med. 2016;9(11):1046–54.
29. Subramanian L, Majeed M. Tulsi: Chemistry and Therapeutic Applications. Sabinsa Corporation; 2019.
30. Hodek P, Trefil P, Stiborová M. Flavonoids—potent and versatile biologically active compounds interacting with cytochromes P450. Chem Biol Interact. 2002;139(1):1–21.
31. El Souda SS, Wahba HE, Mostafa NM, et al. Evaluation of nephroprotective effect of Ocimum sanctum against cisplatin-induced toxicity. J Pharm Pharmacogn Res. 2020;8(4):308–17.
32. Ferreira LA, Almeida JR, Gomez R, et al. Herb–drug interaction between paclitaxel and plant polyphenols: An overview. Phytochem Rev. 2021;20(6):1127–42.
33. Choi JS, Piao YJ. Interaction between flavonoids and CYP enzymes: Impact on herb–drug interactions. Biomol Ther. 2019;27(2):135–40.
34. Kakarala M, Brenner DE, Korkaya H. Targeting breast stem cells with the cancer preventive compounds curcumin and piperine. Breast Cancer Res Treat. 2010;122(3):777–85.
35. Carlson C, Husain K, Mazzio E, et al. Pharmacological modulation of oxidative stress in paclitaxel-treated rats. Toxicol Lett. 2005;155(2):227–36.
36. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
37. Di Renzo G, Maccarrone G, Maffioli E, et al. Pharmacokinetic evaluation of paclitaxel in experimental models. Pharmacol Res. 2019;144:178–89.
38. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis. Comput Methods Programs Biomed. 2010;99(3):306–14.
39. Singh S, Majumdar DK. Effect of fixed oil of Ocimum sanctum on experimental models of gastric ulceration. Planta Med. 1999;65(6):525–7.
40. Wube AA, Rondeau P, Kaushik NK, et al. Herbal extracts altering pharmacokinetics of chemotherapeutics: A systematic overview. Phytother Res. 2022;36(2):828–47.