BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 15, Number 1, April 2026 | Pages: 349-355 | DOI: 10.14421/biomedich.2026.151.349-355 ISSN 2540-9328 (online)

Uncovering the Molecular Mechanisms of *Saurauia vulcani* Korth in Rhodamine B Induced Colon Injury

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Manuscript received: 11 December 2025. Revision accepted: 13 April 2026, Published: 24 April 2026.

Abstract

The illegal food colorant, Rhodamine B (RhB), might lead to chronic colon injury. *Saurauia vulcani* is an ethnomedicine utilized for hepatoprotection, antioxidants, and immunomodulators. The histopathological and bioinformatic assays were conducted to discover the ethanolic extract of *S. vulcani* (EEP) against colon damage in RhB-induced rats. The abnormal results were exhibited in RhB administration, while EEP regained colon length and improved the histopathology of the ascending colon in rats. Furthermore, the construction of PPI predicted TP53, SRC, EGFR, AKT1, MTOR, CASP3, ABCG2, CTNNB1, MAPK14, MAPK8, and JUN as the main targets related to chronic colon injury. The molecular interaction presented *S. vulcani* had the stable fluctuation and strong binding affinities to thymidine phosphorylase. Therefore, this finding could be preliminary data for chronic colon injury treatment.

Keywords: Saurauia; Colorectal; Ethnomedicine; Rhodamine B.

INTRODUCTION

Xenobiotic exposure, for instance to Rhodamine B, tends to promote chronic colon injury by disorganizing the detoxification pathway. Rhodamine B (RhB) is a carcinogen containing nitronium, chlorine, and benzene rings found illegally as the colorant in food at a concentration 10^{-7}M. The absorption of benzene rings and chlorine leads to oxidative stress (Sun et al. 2022), free radicals, and inflammation in the colon (Fujisawa et al. 2025). The elevation of oxidative stress promotes the impairment of the thymidine phosphorylase (TYPH). The enzyme contributes to chemotherapy resistance in colon cancer. This enzyme plays an important role in converting 5-fluorouracil to 5-fluoro-2'-deoxyuridine. However, the mutation of TYPH was overexpressed with angiogenesis (Ribatti 2022), apoptosis, and inhibition of the kinase pathway by tumor necrosis factor (TNF-α) in human colon carcinoma (Paladhi et al. 2022).

Chemotherapy resistance is a challenging treatment problem in colon cancer (Liu et al. 2023). The natural compound has been used regarding its less cytotoxic side effects and good efficacy (Lucchetti et al. 2023) as the therapeutic for colon carcinoma. *Saurauia vulcani* (Actinidiaceae family) is one of the ethnomedicines from Indonesia, known as Pirdot. The herbal tea of *S. vulcani* (Situmorang and Sunandar 2019) was consumed by Batak tribes to relieve some ailments such as diabetes, diarrhea (Gurning et al. 2020), and wound-healing. In addition, the phytochemicals of *S. vulcani* (Pasaribu et al. 2020) contain ursolic acid, oleanolic acid, corosolic acid, maslinic acid, and beta-sitosterol. The phytocompounds of EEP have some protective effect to reduce the damaged histoarchitecture of the spleen (Sinaga et al. 2024b), liver, and kidneys in xenobiotics-exposed rats (Sinaga et al. 2023b).

The preventive effect of EEP has been previously reported in improving the quality of spermatozoa induced by cigarette smoking (Sinaga et al. 2023a), enhancing hematological profile (Lumban Gaol-Adriana et al. 2023), elevating immunostimulatory activities (Sinaga et al. 2022), increasing lymphocyte level (Erlintan Sinaga et al. 2020), and reducing SGOT and SGPT level (Sinaga et al. 2021). However, the therapeutic effects of EEP in Rhodamine B-induced colon are still unclear. Therefore, this study examined the potential treatment of EEP to attenuate colon tissue in RhB-induced rats and predicted the significant role of EEP in chronic colon using a modern pharmacological approach as an underlying for future clinical treatment.

METHODS

Chemicals

Rhodamine B (Sigma, Sigma Aldrich, Singapore) was mixed with sterile water (30%) and administered at 980 mg/kg BW. The histopathological study was measured using Hematoxylin & Eosin 1%. Ethanol 96% was procured from Merck.

Plant materials

The air-dried leaves of *S. vulcani* were obtained from North Tapanuli, North Sumatera, Indonesia. The fresh leaves of *S. vulcani* were rinsed and dried at 40^0 C. The dried leaves were ground using a blender. The simplicial of *S. vulcani* (100 g) was macerated with 96% ethanol (1000 ml) and stirred two days a week at 25^0 C. The extract was filtered and evaporated to acquire 11.5 g of crude ethanol extract. The sample was stored at 4^0 C for further experimental measurement.

Animal and Treatment Design

The protective activity of EEP in RhB exposed to rat colon was conducted by the Institutional Ethics Committees/AREC (License ID: 0453/KEPH-FMIPA/2019) and demonstrated following EU Directive 2010/63/EU for animal treatment (Percie du Sert et al. 2020). This study was executed for 30 days in the Laboratory of Biology of the State University of Medan, Indonesia (Lumban Gaol-Adriana et al. 2023). Twenty-four male rats (190 ± 30 g) (n=6) with a completely randomized design were as follows: (a) Control group (P1); (b) Group II was administered orally RhB 980 mg/kg (P2); (c) Group III received EEP at a dose of 500 mg/kg (P3); (d) Group IV was given RhB 980 mg/kg and EEP 500 mg/kg (P4). On the 31st, all the group treatment was anesthetized using chloroform and dissected in the abdominal cavity. The colon was collected, weighed, and put into the tube with 10% formalin neutral buffer.

The measurement of colon length and histopathological examination

The measurement of colon length is used to identify the colon damage (Rocha et al. 2019). The length of colons was sized adjacent to a standard ruler from the distal end to the colon-cecum junction. Furthermore, the colons were measured using the haematoxylin-eosin method for histopathological examination. All of the colon tissues were fixed and dehydrated in 10% formalin for 24 h. The samples were embedded in paraffin and sectioned at 5-6 µm. The tissues were observed under a light microscope with high resolution at 40× (Dogan et al. 2022).

Data Analysis

The outcome data was presented as mean ± SD. The statistical evaluation was assessed by one-way analysis of variance (ANOVA) followed by Kruskal-Wallis's test using SPSS 22. The significant difference ($p \leq 0.05$) was applied to compare between the treatment groups.

Network Pharmacological Analysis

GeneCards was selected to determine the colon cancer proteins (Yadav et al. 2022). The webserver STRING was set to construct the signal pathway between the target and the constituent of *S. vulcani*. The restricted species "*Homo sapiens*" is applied with a threshold at 0.4. The construction of data was evaluated using Cytoscape 3.8.2.

Docking Study

Docking study could be a potential tool to predict the score affinity and the binding pose. The webserver PubChem was used to identify the phytocompounds of EEP. RCSB database was employed to obtain the structure of thymidine phosphorylase (TP)(PDB:2WK5) (Satpathy et al. 2022). The ligand and protein were prepared for energy minimization, formatted as a "pdbqt" file, and docked using AutoDock Vina 4.1 software. The outcome data was visualized using BIOVIA software.

Dynamic Simulation

Dynamic simulation is needed to demonstrate the fluctuation of protein structures compared to the protein complex interaction in wet laboratories. CABSflex 2.0 (Sinaga et al. 2024a) is used to fluctuate the complex interaction with trajectory frames of 50, a temperature of 1.4 and the distance restraints with default values. RMSF (Root Mean Square Fluctuation) plots indicate the convergence and the flexibility of residue protein active in aqueous solution.

RESULTS AND DISCUSSION

Histopathological examination and Colon length

As presented in **Fig. 1**, the histopathology of the ascending colon in each group was changed. Our finding showed that the normal histology of the ascending colon was found in the control group and the P3 group. The RhB group exhibited the mucosal epithelial destruction, the scattered goblet cells, abnormal crypts, the submucosal invasion, and mild dysplasia. However, EEP significantly ($p \leq 0.05$) reduced the ascending colon damage in RhB exposure to rats. The administration of EEP is a significant ($p \leq 0.05$) improvement on the histopathological alterations compared to the P2 group. The RhB-treated group resulted in damaged mucosal epithelium, scattered goblet cells, and abnormal crypts in colon tissue. The EEP improve the degree of severity in the ascending colon in the P4 group. As displayed in **Fig. 2**, the length of the colon in the P2 group was significantly shorter than in the control group. However, the administration of EEP significantly ($p \leq 0.05$) lengthens the colon in P4 groups.

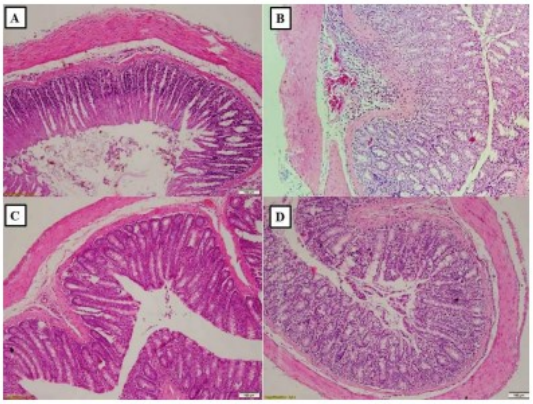

Figure 1. Histopathological of the ascendent colon in rats (a) Control Group P1; (b) RhB groups 980 mg/kg; (c) EEP groups 500 mg/kg; (d) RhB + EEP groups (40 x magnification).

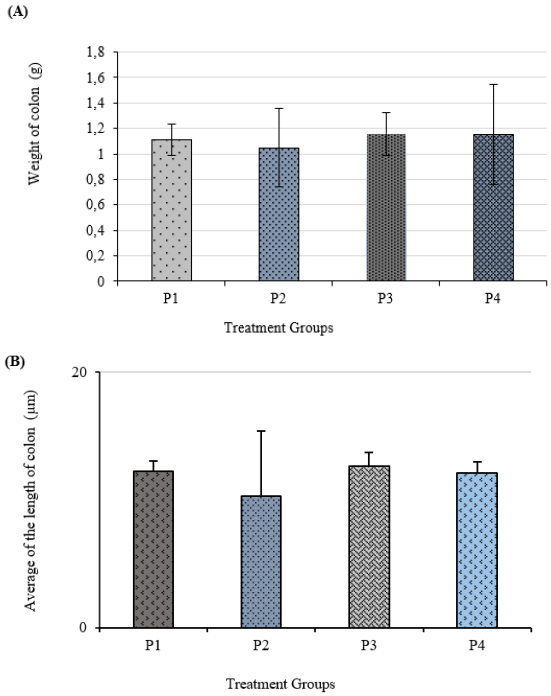

Figure 2. Effect of EEP on weight (A) and length of colon (B) in Rhodamine B induced rats.

Network Pharmacological Analysis

As shown in **Fig.** 3, the PPI network with a confidence level of 0.40 predicted 59 nodes and 532 edges in the pathway of the EEP phytocompounds against colon carcinoma. The top eleven genes were TP53, SRC, EGFR, AKT1, MTOR, CASP3, ABCG2, CTNNB1, MAPK14, MAPK8, and JUN, which tend to be the core target. As displayed in **Table 1,** this study evaluated PI3K-Akt signal transduction pathways in cancer, the MAPK pathway, colorectal cancer, the P53 signaling pathway, and apoptosis.

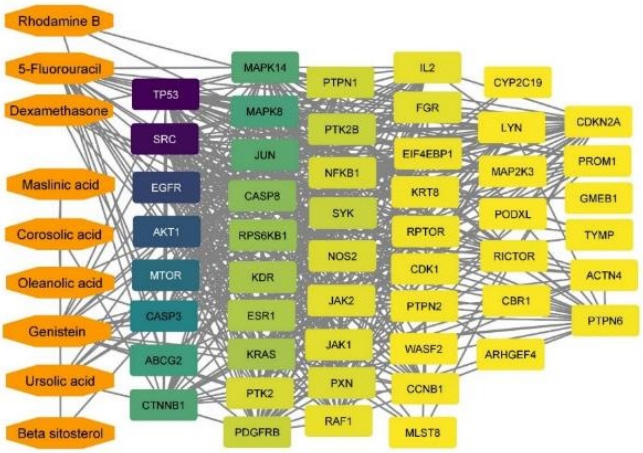

Figure 3. *S. vulcani* bioactive compound -target network construction against Rhodamine B-induced colon carcinoma**.**

Table 1. Pathway interaction between bioactive *Saurauia vulcani* and acute colon injury exposed to Rhodamine B.

Pathway ID	Pathway description	Count in gene set	False discovery rate	Gene
04151	PI3K-Akt signaling pathway	17	9.02e-15	NFKB1, IL2, SYK, JAK2, JAK1, KDR, PTK2, RAF1, EGFR, PDGFRB, TP53, MTOR, AKT1, RPTOR, MLST8, EIF4EBP1, RPS6KB1
05200	Pathways in cancer	16	6.8e-14	NOS2, CDKN2A, NFKB1, JUN, JAK1, CASP3, CASP8, CTNNB1, AKT1, MTOR, MAPK8, TP53, EGFR, PTK2, RAF1, PDGFRB
04010	MAPK signaling pathway	11	2.76e-09	NFKB1, JUN, CASP3, RAF1, MAPK8, EGFR, AKT1, TP53, PDGFRB, MAP2K3, MAPK14
05210	Colorectal cancer	7	4.89e-09	CASP3, JUN, CTNNB1, AKT1, MAPK8, TP53, RAF1
04115	P53 signaling pathway	5	7.58e-06	TP53, CASP3, CASP8, CCNB1, CDKN2A
04210	Apoptosis	5	2.16e-05	TP53, AKT1, CASP3, CASP8, NFKB1

Molecular Docking and dynamic analysis

As listed on **Table 1**, the confirmation of the bioactive EEP bound to protein thymidine phosphorylase was found with ranges of -8.0 to -13.5 kcal/mol. The EEP compounds, for instance maslinic acid, bound to thymidine phosphorylase (**Fig. 4A**) with docking scores of -13.5 kcal/mol and formed the hydrogen bond at residues Ala272, Asp274, Lys275, Glu390, and Arg464 and hydrophobic interaction at Asp274, Lys275, Leu391, Val427, Pro470, and Pro472. In comparison, 5-Fluorouracil (-6.0 kcal/mol) as the control drug formed hydrogen bonds at Thr118, Gly145, and Thr154.

Molecular dynamic simulation was evaluated on the movements of protein residues using the fluctuation plot (RMSF) (Silitonga et al. 2024). The TP- EEP complexes showed the fluctuation in RMSF value from 1.59 Å to 4.19 Å. As shown in **Fig. 4B**, the RMSF plot had the highest mobility at Pro33, Gly47, Ala320, Pro373, Pro472, and Pro479.

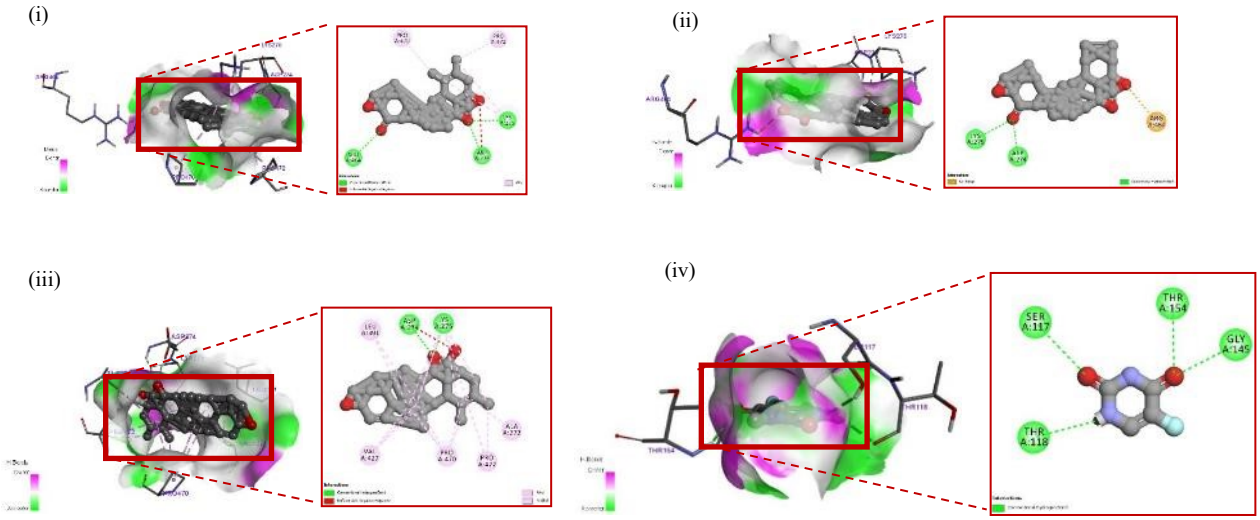

Figure 4A. Molecular docking study of Protein Thymidine phosphorylase and bioactive compound Pirdot;(i) Corosolic acid; (ii) Maslinic acid; (iii) Ursolic acid; (iv) 5-Fluorouracil.

Table 2. Molecular docking results of bioactive compound of S. vulcani and 5-Fluorouracil bound to Thymidine phosphorylase.

Compound	Protein Thymidine Phosphorylase		
	Binding Affinity (kcal/mol)	Hydrogen bond	Hydrophobic interaction
Corosolic Acid	-13.3	Asp274, Lys275, Glu390, Arg464	Asp274, Lys 275, Leu391, Val427, Pro470, Pro472
Genistein	-9.4	His116, Gly145, Thr154, Lys221	-
Maslinic acid	-13.5	Ala272, Asp274, Lys275, Glu390, Arg464	Asp274, Lys 275, Leu391, Val427, Pro470, Pro472
Oleanolic acid	-8.0	Glu189	Arg146, Pro193, Tyr199
Beta sitosterol	-10.4	Gly147	Arg146, Ile197, Tyr199, Ala200
Ursolic acid	-13.4	Ala272, Asp274, Lys275, Glu390, Arg464	Asp274, Lys 275, Leu391, Val427, Pro470, Pro472
5-Fluorouracil	-6.1	Thr118, Gly145, Thr154	-

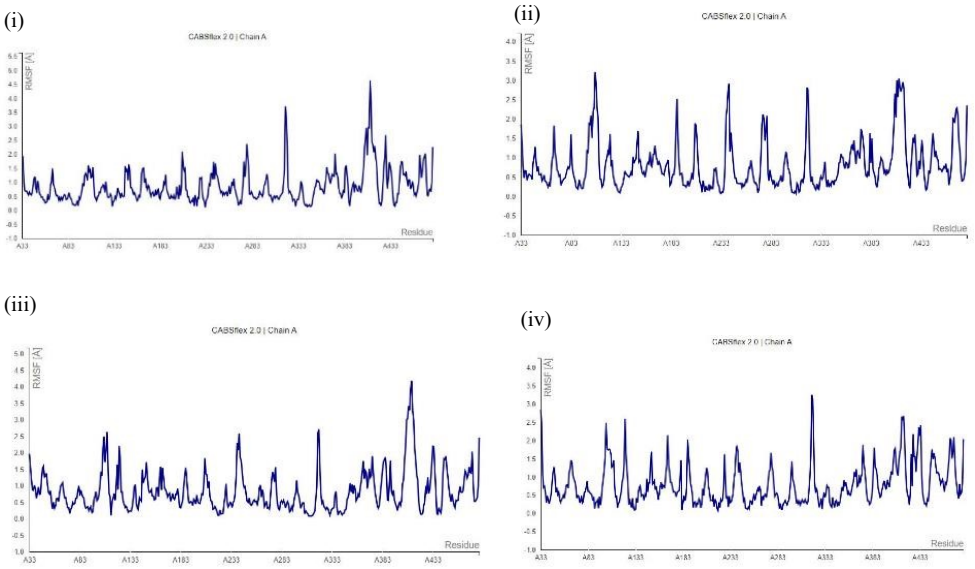

Figure 4B. RMSF plot of Protein Thymidine phosphorylase and bioactive compound Pirdot;(i) Corosolic acid; (ii) Maslinic acid; (iii) Ursolic acid; (iv) 5-Fluorouracil.

Discussion

RhB has been used as an illegal food colorant in Indonesia (Rahmawati et al. 2020) due to xenobiotics containing chlorine and benzene (Sulistina and Martini 2020). These compounds caused chronic colon progression in rats through the signaling of reactive oxygen species (ROS)(Sarmiento-Salinas et al. 2021). While gemcitabine has chemotherapy insensitivity in colon cancer (Yu et al. 2021), medicinal plants, notably EEP, tend to support the drug development against RhB-induced colon damage. The accumulation of RhB contributed to invading the colorectal preneoplasia morphology through the degree of inflammation. The severity of the histological damage caused gene mutation and the proliferation of crypt cells. In addition, glutathione S-transferases (GST) might be an important key to regulating cell proliferation, fibrogenesis, and apoptosis in phase II xenobiotic metabolism (Li et al. 2023). Additionally, 4-hydroxynonenal is positively metabolized by glutathione S-transferase alpha 4 (GSTA4) to suppress mutagenic reactive oxygen and inflammatory cytokines in colorectal cancer development (Ma et al. 2023).

The EEP has pharmacological effects on colon cancer via 11 hub top genes, including TP53, SRC, EGFR, AKT1, MTOR, CASP3, ABCG2, CTNNB1, MAPK14, MAPK8, and JUN. This research was similar to the previous study, which indicated that overexpression of genes, such as TP53, PODXL, BCL7B, ARHGEF4, WAVE2, ACTN4, KRAS, CDKN2A, and SMAD4, correlates to metabolic reprogramming in colon cancer development. Our finding discovered that the phytocompounds of EEP have the ameliorative effect against RhB-induced chronic colon injury, which regulated the PI3K-Akt signaling pathway, MAPK signaling pathway, P53 signaling pathway, and apoptosis.

The benzene ring of RhB leads to stimulated apoptosis through the MAPK signaling pathway in colorectal cancer (Hu et al. 2022). Besides, the benzene ring interacts with receptor tyrosine kinase (RTK), which plays an important role in the phosphatidylinositol 3-kinase (PI3K) signaling cascade mediators (Taruneshwar Jha et al. 2023). Besides, thymidine phosphorylase might be a prominent xenobiotic metabolizing enzyme to induce angiogenesis in metastatic colorectal cancer (Sperotto et al. 2021). Our research demonstrated that EEP has a good interaction to bind thymidine phosphorylase. Moreover, the chemopreventive mechanism of EEP might play an important underlying role for future clinical research.

CONCLUSION

To conclude, the potential of EEP against chronic colon improved colon length in RhB-induced rats. The preventive effect of EEP relieved the architecture of the ascending colon. Modern pharmacological analysis suggested the EEP regulated the activity of colon carcinoma through the TP53, SRC, EGFR, AKT1, MTOR, CASP3, ABCG2, CTNNB1, MAPK14, MAPK8, and JUN genes. Overall, these results could be a reference for future development of colon carcinoma therapeutics.

Acknowledgement: The author would like to thank for material and laboratory support from State University of Medan.

Authors' Contributions: Feimmy Ruth Pratiwi Sipahutar took writing-original draft, software, visualization and validation; Erlintan Sinaga supervised conceptualization, methodology, and resources; Masdiana Sinambela carried out data curation and resources; Adriana Yulinda Dumaria LumbanGaol performed validation and formal analysis; Melati Nugrahalia Sipahutar made project administration, visualization and data curation.

Competing Interest: The authors declare that there are no competing interests.

Funding: The authors declare there is no funding for this study.

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