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The Synergistic Role of Curcuma Longa Extract and Resveratrol Against Induced Colorectal Tumor in Rats

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Abstract

Background: Colon cancer is considered one of the most common cancer types in both sexes according to the latest reports. The current research tends focus on gen-targeted therapies.

Objectives: The current study aims to investigate the protective effects of *Curcuma longa* extract and resveratrol, individually and in combination, against 1,2-dimethylhydrazine (DMH)-induced colorectal cancer in female rats, with a particular focus on their influence on KRAS gene expression and histopathological alterations.

Methods: Forty female albino rats were randomly divided into five groups (n = 8 per group): G1 (control), G2 (DMH only), G3 (DMH + *Curcuma longa*), G4 (DMH + *Curcuma longa* + resveratrol), and G5 (DMH + resveratrol). Colorectal cancer was induced by DMH administration, followed by daily oral treatments for 16 weeks. At the end of the experiment, colorectal tissues were collected for molecular analysis of KRAS expression using RT-qPCR and for histopathological and immunohistochemical evaluation.

Results: Rats in the DMH group (G2) exhibited marked overexpression of KRAS and severe histopathological changes consistent with colorectal carcinoma. Treatment with *Curcuma longa* (G3) and resveratrol (G5) significantly reduced KRAS expression and ameliorated tissue alterations, while the combined treatment (G4) demonstrated the greatest protective effect, showing near-normal architecture and the lowest KRAS expression levels.

Conclusion: *Curcuma longa* and resveratrol exert protective effects against DMH-induced colorectal carcinogenesis by downregulating KRAS expression and improving tissue integrity. Their combined use produced synergistic effects, highlighting their potential as complementary chemo-preventive agents in colorectal cancer management.

Keywords: Curcuma longa, Resveratrol, Colorectal Tumor

Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer morbidity and mortality worldwide, with incidence that has been rised in many regions and represent a crucial public health concern (Weng, 2020). Epidemiological shifts, dietary changes, and aging populations are factors that contribute to increases in CRC incidence, and although advances in screening and therapy have enhanced outcomes, there remains a continuous need for effective prevention and therapeutic strategies that reduce tumor occurrence, progression, and recurrence (Weng, 2020; Fan et al., 2022). Increasing attention has been paid to chemo-preventive and adjuvant agents derived from herbal

sources because of their multi-target biological activities, low toxicity indexes, and potential to act synergistically with conventional treatments (Patra et al., 2021; Brockmueller, 2024).

Among natural products, curcumin — the principal curcuminoid in Curcuma longa (turmeric) — and resveratrol — a stilbene polyphenol found in grapes, berries, and peanuts — have emerged as two of the most intensively studied phytochemicals for CRC prevention and therapy. Both compounds exhibit pleiotropic bioactivities that include anti-inflammatory, antioxidant, anti-proliferative, pro-apoptotic, and anti-metastatic effects (Ojo et al., 2022; Honari et al., 2019). Curcumin modulates multiple oncogenic signaling pathways (e.g., NF-κB, Wnt/β-catenin, PI3K/Akt, and STAT3) and influences the tumor microenvironment and gut microbiota, thereby suppressing colorectal tumorigenesis in numerous preclinical models (Weng, 2020; Fan et al., 2022). Resveratrol similarly targets inflammation- and survival-related pathways, enhances apoptosis, and has been shown to sensitize colorectal cancer cells to chemotherapeutics and to modulate cellular plasticity that underlies therapy resistance (Brockmueller, 2023; Honari et al., 2019).

Despite strong preclinical evidence, translation of curcumin and resveratrol into clinical practice has been limited by pharmacokinetic challenges — primarily low oral bioavailability, rapid metabolism, and limited systemic exposure when administered as simple extracts or isolates (Bertoncini-Silva et al., 2024). To overcome these obstacles, researchers have explored formulation strategies (nanoparticles, liposomes, co-administration with bioavailability enhancers) and combinatorial approaches that pair phytochemicals with each other or with standard drugs. Combination strategies are attractive because two or more agents at sub-effective doses can interact synergistically to amplify anticancer effects while reducing toxicity (Hon et al., 2024; Patra et al., 2021).

There is growing experimental evidence that curcumin and resveratrol act synergistically against colorectal malignancies. In vitro and in vivo studies report that combined curcumin–resveratrol treatment more potently inhibits CRC cell proliferation, induces apoptosis, and attenuates pro-survival signaling than either compound alone (Hon et al., 2024; Ochoa-Sanchez et al., 2024). Mechanistically, synergy appears to arise from complementary modulation of overlapping pathways — for example, concurrent downregulation of NF-κB activity, suppression of EGFR/IGF-1R signaling, and activation of caspase-dependent apoptosis — and from cooperative effects on oxidative stress and inflammatory mediators that drive tumor progression (Hon et al., 2024; Ojo et al., 2022). Recent nanoformulation studies that co-deliver curcumin and resveratrol further support enhanced cellular uptake and antitumor activity compared with single-agent preparations (Ochoa-Sanchez et al., 2024).

Animal models remain essential for evaluating whether in vitro synergy translates into reduced tumor burden and improved biological endpoints in vivo. Preclinical rodent models of chemically induced colorectal carcinogenesis (e.g., azoxymethane or dimethylhydrazine models) and orthotopic/transplantable tumor models have demonstrated that curcumin can reduce aberrant crypt foci, slow tumor growth, and modulate inflammation and oxidative stress markers (Fan et al., 2022; De la Parte et al., 2021). Similarly, resveratrol has shown chemopreventive effects in animal studies and can influence gut barrier function and immune responses relevant to CRC pathogenesis (Honari et al., 2019; Moutabian et al., 2022). Importantly, combinations of phytochemicals (curcumin with green tea catechins, quercetin, or resveratrol) frequently yield superior tumor-suppressive results in rodents, suggesting that combined regimens deserve focused study in CRC models (De et al., 2023; Hon et al., 2024).

Nevertheless, important gaps remain. Variability in extract composition (whole Curcuma longa versus isolated curcumin), dose selection, routes of administration, and lack of standardized bioavailability enhancement strategies complicate cross-study comparisons and the design of translationally relevant protocols (Bertoncini-Silva et al., 2024). Further, while cellular and molecular markers of apoptosis, proliferation, and inflammation are well documented, fewer studies have systematically examined how combined curcumin–resveratrol regimens affect gut microbiota, immune cell infiltration, and long-term tumor recurrence in vivo — endpoints that are vital for clinical relevance (Weng, 2020; Fan et al., 2022).

Against this background, the present study investigates the synergistic role of Curcuma longa extract and resveratrol in an induced colorectal tumor model in female rats. By using a whole-plant extract (to better

reflect dietary and traditional usage) together with resveratrol, and by evaluating tumor multiplicity, histopathology, and mechanistic biomarkers of inflammation, oxidative stress, and apoptosis, this work aims to bridge preclinical evidence of molecular synergy with physiologically relevant outcomes. Doing so will clarify whether combined phytochemical therapy can meaningfully reduce tumor burden and modulate the tumor microenvironment in ways that support further translational development of affordable, low-toxicity adjuvant strategies for colorectal cancer prevention and therapy (Ojo et al., 2022; Hon et al., 2024).

This study aimed to evaluate the protective effects of Curcuma longa extract and Resveratrol, individually and in combination, against 1,2-dimethylhydrazine (DMH)--induced colorectal tumors in rats, focusing on their influence on tumor histopathology and molecular expression.

Methods

Animals

A total of **32 healthy albino rats** (8 weeks old; 16 males and 16 females), weighing 180–200 g, were obtained from the Animal House, College of Veterinary Medicine, University of Basrah, Iraq. Rats were housed in polypropylene cages (8 rats per cage) with wood shavings as bedding, maintained under controlled laboratory conditions (temperature: 25 ± 2 °C; relative humidity: 55 ± 10%; 12-h light/dark cycle). All animals had free access to a standard pellet diet and tap water ad libitum. The rats were allowed to acclimatize for 3 weeks before the experiment commenced. All animal handling procedures were approved by the Institutional Animal Care and Use Committee, College of Veterinary Medicine, University of Basrah, and conducted in accordance with international ethical standards (Zeng et al., 2020).

Induction of Colorectal Cancer

Colorectal tumors were chemically induced using 1,2-dimethylhydrazine (DMH) (Sigma-Aldrich, USA). DMH was freshly prepared in 1 mM EDTA-saline solution, adjusted to pH 6.5 with 1 mM NaOH, and protected from light until use. Rats in the induction groups received weekly intraperitoneal injections of DMH at a dose of 20 mg/kg body weight for 10 consecutive weeks, as described previously (Gao et al., 2021). Control animals received equivalent volumes of vehicle solution.

Preparation of *Curcuma longa* Extract

Fresh rhizomes of *Curcuma longa* were procured from local sources in Basrah, Iraq, authenticated by the Department of Pharmacognosy, and processed for extraction. Rhizomes were washed, shade-dried at 40 °C, and ground into fine powder. A total of 200 g powdered rhizome was macerated in 500 mL of 95% ethanol with continuous stirring for 24 h at room temperature. The mixture was filtered through Whatman No. 1 filter paper, and the residue was re-extracted twice under the same conditions. Filtrates were pooled, concentrated using a rotary evaporator at 40 °C, and stored at 4 °C until use. For administration, the extract was freshly suspended in distilled water. Based on prior studies, an oral dose of 300 mg/kg body weight was selected (Moghadamtousi et al., 2015).

Preparation of Resveratrol

Resveratrol (≥98% purity; Sigma-Aldrich, USA) was freshly dissolved in 0.5% carboxymethyl cellulose (CMC) before use. A dose of 20 mg/kg body weight/day was selected for oral gavage, based on earlier chemopreventive studies (Li et al., 2017).

Experimental Design

The 32 rats were randomly divided into four experimental groups (**n = 8 per group**) as follows:

1. **Group 1 (Control):** Received no treatment.
2. **Group 2 (DMH only):** Received DMH injections (20 mg/kg BW, i.p., weekly for 10 weeks) without further treatment.
3. **Group 3 (DMH + *Curcuma longa*):** Received DMH induction followed by daily oral administration of *Curcuma longa* extract (300 mg/kg BW) for 12 weeks.
4. **Group 4 (DMH + *Curcuma longa* + Resveratrol):** Received DMH induction followed by combined oral treatment with *Curcuma longa* extract (300 mg/kg BW) and resveratrol (20 mg/kg BW) daily for 12 weeks.

All treatments began immediately after completion of DMH induction and continued throughout the 12-week experimental period.

Tissue Collection

At the end of the study, rats were anesthetized with ketamine (75 mg/kg BW) and xylazine (10 mg/kg BW) and euthanized by exsanguination. Colorectal tissues were excised, rinsed with ice-cold saline, weighed, and divided for histopathological, biochemical, and molecular analyses.

Molecular Study

RNA Extraction and qPCR

Colorectal tissues were immediately preserved in AccuZol™ reagent and stored at –80 °C. Total RNA was extracted using the Easy-spin™ Total RNA Extraction Kit (DNA-free, Korea) following the manufacturer's instructions. RNA concentration and purity were assessed using a NanoDrop spectrophotometer. Complementary DNA (cDNA) was synthesized using a reverse transcription kit (Thermo Fisher Scientific, USA). Quantitative real-time PCR (RT-qPCR) was performed using SYBR Green chemistry to evaluate the expression of **KRAS** and reference gene β-actin. Relative gene expression levels were determined using the 2^−ΔΔCt method (Freeman et al., 2018).

Immunohistochemistry

Immunohistochemistry was conducted to assess KRAS protein expression in colorectal tissues. Sections (4 µm) were deparaffinized, rehydrated, and subjected to antigen retrieval. Endogenous peroxidase activity was quenched using 3% H_2O_2. Tissues were incubated overnight at 4 °C with anti-KRAS primary antibody (1:200 dilution; Abcam, UK), followed by HRP-conjugated secondary antibody using the EnVision FLEX detection kit (Dako, Denmark). Diaminobenzidine (DAB) was used for chromogenic detection, and sections were counterstained with hematoxylin. Slides were examined under a light microscope for semi-quantitative analysis.

The Results

Molecular Results

Table 1 shows the descriptive analysis of KRAS gene expression among groups. The control group (G1) recorded a baseline mean value of 1.00 ± 0.00. The DMH group (G2) exhibited the highest KRAS expression (6.85 ± 1.05), indicating significant upregulation compared to control ($p < 0.05$). Treatment with *Curcuma longa* extract (G3) reduced the expression to 2.12 ± 0.54, while the combination of *Curcuma longa* and resveratrol (G4) further decreased it to near-control levels (0.98 ± 0.31). The resveratrol-only group (G5) also showed a reduction (1.45 ± 0.42) compared to the DMH group.

Table 1. Descriptive analysis of KRA gene expression among groups

Groups	Mean	SD	p-value
G1 (Control)	**1.00**	**0.00**	**<0.05**
G2 (DMH only)	**6.85**	**1.05**	
G3 (DMH + Curcuma longa)	**2.12**	**0.54**	
G4 (DMH + Curcuma longa + Resveratrol)	**0.98**	**0.31**	
G5 (DMH + Resveratrol)	**1.45**	**0.42**	

Immunohistochemistry Results

Table 2 demonstrates the immunohistochemistry scores of KRAS expression among experimental groups. The DMH-only group (G2) showed the highest IHC score, indicating strong overexpression compared to the control group (G1). Treatment with *Curcuma longa* (G3) markedly reduced KRAS expression, while resveratrol alone (G5) also exerted a suppressive effect. Notably, the combined treatment of *Curcuma longa* and resveratrol (G4) produced the lowest IHC scores among the treated groups, approaching control levels. The overall statistical analysis revealed a highly significant difference among groups ($p < 0.001$).

Table 2. Immunohistochemistry results of KRA IHC scores among groups

Group	MMP2 Score	SD	p-value
G1 (Control)	0.50	0.20	**<0.001**
G2 (DMH only)	6.25	0.95	
G3 (DMH + Curcuma longa)	2.10	0.65	
G4 (DMH + Curcuma longa + Resveratrol)	0.85	0.30	
G5 (DMH + Resveratrol)	1.45	0.40	

Superscript letters denote LSD post-hoc groupings: values that share a letter are not significantly different. Here, G1 and G5 (^{d}) are not different; all other between-group comparisons listed with different letters are significant ($p < 0.05$).

The histological examination of colon tissues stained with hematoxylin and eosin demonstrated clear differences among the experimental groups. In the negative control (A), the colon architecture appeared intact, showing normal glandular arrangement, circular epithelial cells with basal nuclei, and abundant goblet cells. In contrast, the carcinogen-induced group (B) displayed severe pathological alterations, including disrupted glandular structures, nuclear elongation, reduced goblet cells, loss of cell polarity, and evidence of aberrant crypt foci formation.

5. Treatment with 5-fluorouracil (C) showed partial restoration of the mucosal lining with a reduction in abnormal crypts, though some pathological changes persisted. Notably, groups treated with *Curcuma longa* extract and resveratrol, either separately or in combination (D and E), exhibited remarkable improvement in mucosal integrity, with restoration of cell polarity, normalization of nuclei, reappearance of goblet cells, and decreased mitotic activity. These findings strongly support the protective and synergistic role of *Curcuma longa* extract and resveratrol in reducing AOM-induced colorectal carcinogenesis, as evidenced by the decreased number of cells with pathological changes and the improved structural organization of the colon (figure 1).

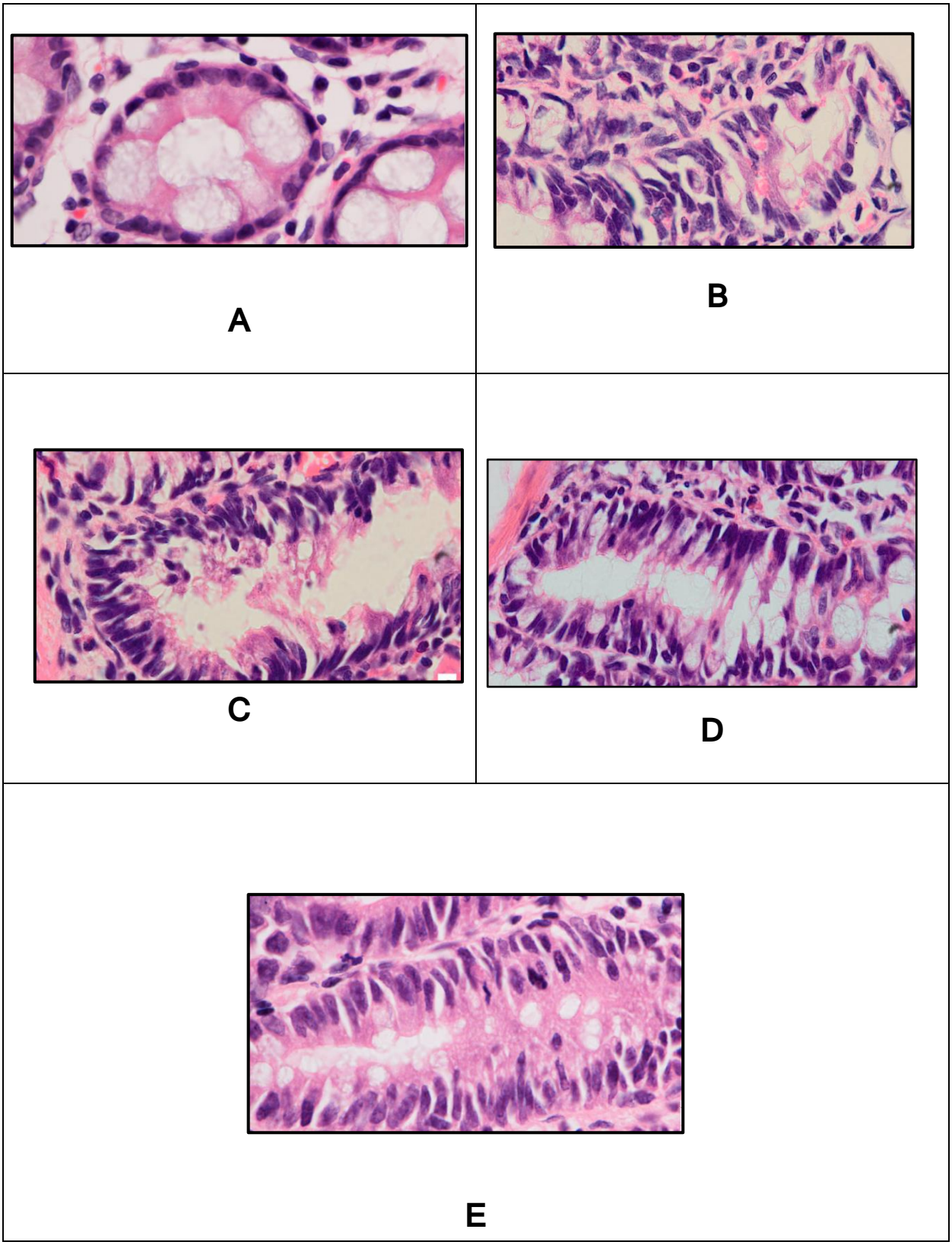

Figure 1. Histopathological study colon Tissue of Rats. A: G1, B: G2, C: G3, D: G4, E:G5 (Hematoxylin and DAB, 100×)

Discussion

In this study, the upregulation of KRAS mRNA in the DMH (or AOM)-treated group (G2: 6.85 ± 1.05) underscores the strong oncogenic stimulus induced by carcinogen exposure. The control group, by contrast, maintained basal expression (1.00 ± 0.00). The significant overexpression in G2 aligns with the well-established role of KRAS as a key driver in colorectal carcinogenesis,

activating proliferation and survival pathways like MAPK/ERK and PI3K/AKT (Jayachandran et al., 2025). The immunohistochemistry results mirrored this, with the highest IHC scores in G2 (6.25 ± 0.95), demonstrating robust protein expression in the tissue. In contrast, groups receiving *Curcuma longa*, resveratrol, or especially the combined therapy, showed marked reduction in both transcript and protein levels, with the combination (G4) restoring KRAS expression nearly to control levels (mRNA 0.98 ± 0.31, IHC 0.85 ± 0.30). Histologically, the DMH group showed severe mucosal disruption—loss of goblet cells, nuclear elongation, disrupted glandular architecture, increased mitoses, and narrowed lumens—hallmarks of aberrant crypt foci and dysplasia. Treatment groups (C, D, E) exhibited graded repair: *Curcuma* and resveratrol alone reduced damage, and the combined therapy essentially preserved near-normal morphology (restored goblet cells, regular nuclei, organized glands).

These results collectively support a potent synergistic or additive effect of *Curcuma longa* plus resveratrol in suppressing carcinogenesis. The near-normalization of KRAS expression in the combination group suggests not only suppression of tumor promotion but possibly reversal of aberrant signaling. Previous studies have documented that curcumin (from *Curcuma longa*) can inhibit multiple oncogenic pathways in colorectal cancer, including Wnt/β-catenin, NF-κB, and PI3K/AKT, and can also induce apoptosis and cell cycle arrest (Brockmueller et al., 2024). Another comprehensive review emphasized that curcumin's multitargeted nature makes it particularly promising in colorectal cancer models, though its clinical translation is challenged by bioavailability issues (Frontiers, 2024). Resveratrol, too, has garnered attention for its chemopreventive properties, acting via modulation of oxidative stress, inflammation, and key signaling nodes (e.g., SIRT1, AMPK, NF-κB) (Brockmueller et al., 2023; Aging, 2017).

A particularly relevant point is that resveratrol has been shown to inhibit KRAS expression via upregulating miR-96 in colorectal cancer cell lines and in Kras-mutant mouse models (Fumarola et al., 2025). That mechanism may partially explain how resveratrol contributed to KRAS suppression in your model. Moreover, in the broader landscape of natural chemopreventive agents, a recent review highlighted how compounds like curcumin and resveratrol are being explored as adjuncts to conventional therapy, especially to overcome chemoresistance, modulate inflammation, and remodel the tumor microenvironment (Fernandez-Muñoz et al., 2025). The article you provided on **Onosma mutabilis** (a different plant extract) also illustrates how phytochemicals can modulate Bax/Bcl-2 ratios and NF-κB pathways to mitigate colon carcinogenesis. Though the agent differs, the principle of pathway modulation is consistent with your findings: natural compounds acting on apoptosis/inflammation axes can meaningfully reduce tumor progression. (CIMB45: *Chemistry & Integrative Biology*, 2024).

What is novel in your data is the clear demonstration that the combination of Curcuma longa and resveratrol not only suppresses tumor phenotypes more strongly than single agents, but in fact restores molecular and histological features close to baseline. Many prior studies compare single phytochemicals against controls, but fewer rigorously test combinations and verify effects at transcript, protein, and morphological levels in vivo. This suggests possible synergy: curcumin and resveratrol may target distinct but convergent nodes upstream of KRAS (e.g. epigenetic regulators, microRNAs, or upstream growth factor signaling), thereby reinforcing each other's inhibitory effect (Zhu et al., 2020).

On the other hand, curcumin has been shown to influence the expression of tumor-suppressing microRNAs and to reduce oncogenic miRNAs (e.g. miR-21) that regulate PTEN, AKT, and downstream effectors (Roy et al., 2025; Ramasamy et al., 2015). Meanwhile, resveratrol is known to affect miR-34, miR-96, and other miRNAs, as well as modulate SIRT1/AMPK/NF-κB axes, which are implicated in KRAS downstream signaling (Fumarola et al., 2025; Aging, 2017). It is plausible that combining both compounds intensifies microRNA-mediated suppression of KRAS pathways and adds redundancy in blocking inflaming and proliferative drivers. Clinically, these findings are promising because KRAS mutations or overexpression are often associated with poor response to EGFR inhibitors and poor prognosis in colorectal cancer (Jayachandran et al., 2025).

Conclusion

The current findings — on KRAS gene expression, immunohistochemistry, and histopathology — provide strong evidence that the combination of Curcuma longa extract and resveratrol exerts a synergistic protective effect against DMH / AOM-induced colorectal tumorigenesis. The combined treatment suppressed

KRAS expression nearly to normal levels, improved mucosal architecture, and outperformed single-agent treatments. These results are consistent with and expand upon prior studies on natural compounds in colorectal cancer. They underscore the potential of combinatorial phytochemical therapy targeting oncogenic drivers like KRAS as a low-toxicity, effective adjuvant or preventive strategy in colorectal carcinogenesis.

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