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EXPERIMENTAL COLORECTAL CARCINOGENESIS IN ALBINO WISTAR RATS: INCIDENCE, TUMOUR BURDEN, AND INDUCTION SUCCESS RATE FOLLOWING 1,2-DIMETHYLHYDRAZINE EXPOSURE — REVIEW

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ABSTRACT

Background: Colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality worldwide. To better understand colorectal carcinogenesis and evaluate chemopreventive interventions, chemically induced animal models are essential. Among these, the 1,2 dimethylhydrazine (DMH)-induced colorectal cancer model in albino Wistar rats is particularly valuable, as it closely mimics the histopathological and molecular characteristics of human sporadic CRC. **Objective:** This systematic review aims to evaluate the incidence rate, tumor burden, induction success, histopathological progression, and molecular characteristics of DMH-induced colorectal carcinogenesis in albino Wistar rats. **Methods:** We conducted a systematic review following PRISMA 2020 guidelines. A comprehensive literature search was performed across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar for studies published

between 2000 and 2025. We included experimental studies focusing on DMH-induced colorectal cancer in albino Wistar rats. Data extracted included induction protocols, tumor incidence, aberrant crypt foci (ACF) formation, adenoma occurrence, adenocarcinoma prevalence, and molecular alterations. **Results:** Thirty-six eligible studies were included in the final synthesis. Across these studies, DMH doses ranged from 20 to 40 mg/kg, administered either subcutaneously or intraperitoneally over 8 to 20 weeks. The model proved highly reliable, with tumor induction success rates varying between 68% and 100%, and adenocarcinoma incidence ranging from 55% to 95%. Aberrant crypt foci were detected in nearly all DMH-treated subjects. Consistent molecular findings included heightened oxidative stress, β-catenin accumulation, cyclooxygenase-2 (COX-2) overexpression, inflammatory cytokine activation, and DNA methylation abnormalities. **Conclusion:** The DMH-induced colorectal carcinogenesis model in albino Wistar rats is highly reproducible and carries substantial translational relevance for human CRC research. Its high tumor induction rates and predictable histopathological progression make it an excellent platform for preclinical therapeutic investigations.

KEYWORDS: Colorectal cancer, DMH, Wistar rats, tumor incidence, carcinogenesis, aberrant crypt foci, PRISMA systematic review.

1. INTRODUCTION

Colorectal cancer represents the third most frequently diagnosed malignancy globally and stands as a primary driver of cancer-associated mortality. The disease typically develops through a well-documented adenoma-carcinoma sequence, characterised by the progressive accumulation of genetic and epigenetic alterations that ultimately trigger the malignant transformation of colonic epithelial cells.[7]To elucidate the complex biology of colorectal tumours, experimental animal models remain indispensable.[9,10] Among the various chemically induced models, 1,2-dimethylhydrazine (DMH) is widely recognised as a highly potent, colon-specific carcinogen capable of generating lesions that virtually mirror human colorectal neoplasia.[1,6] Following administration, DMH undergoes hepatic biotransformation into methylazoxymethanol and methyl diazonium ions. These reactive metabolites induce targeted DNA alkylation, oxidative injury, and mutagenesis within the colon.[1,6] Over time, these cellular insults drive aberrant crypt formation, adenomatous changes, and, eventually, invasive adenocarcinoma. This systematic review synthesises the

current evidence regarding the incidence rates, tumour burden, induction success, and pathological outcomes of DMH-induced colorectal carcinogenesis in albino Wistar rats.

2. MATERIALS AND METHODS

Protocol-This systematic review was structured and conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Eligibility Criteria

Category	Criteria
Inclusion criteria	Experimental studies utilising albino Wistar rats; models specifically using DMH-induced colorectal carcinogenesis, studies reporting histopathological and molecular evaluations; full-text publications available in English.
Exclusion criteria	Studies involving non-rat models or different rat strains; in vitro investigations; review articles, letters, or editorials; primary studies lacking clear tumour incidence data.

Search Strategy

A comprehensive literature search was executed across five major databases: PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search syntax utilised combinations of the following terms: "DMH induced colorectal cancer," "1,2-dimethylhydrazine," "Wistar rats," "experimental colon carcinogenesis," "tumour incidence," and "aberrant crypt foci."

Data Extraction: Variables extracted from the selected literature included sample size, DMH dosage, route of administration, study duration, tumour incidence and multiplicity, histological grading, and specific molecular markers evaluated.

3. RESULTS

PRISMA Flow Sequence

The study selection process proceeded as follows:

- Records initially identified through database searching: n = 612
- Records remaining after duplicate removal: n = 548
- Records excluded during initial screening: n = 441
- Full-text articles assessed for eligibility: n = 107
- Full-text articles excluded based on criteria: n = 71
- Final studies included in qualitative synthesis: n = 36.

Table 1: Characteristics of Key Included Studies

These five DMH studies used doses from 20–40 mg/kg over 7–20 weeks and produced high tumor incidence (85–100%), demonstrating that DMH reliably induces colon lesions ranging from ACF and dysplasia to adenoma and adenocarcinoma in Wistar rat models.[1,5] The findings support dose- and time-dependent progression of colorectal carcinogenesis, with higher doses and longer durations generally associated with advanced pathology (severe dysplasia/adenocarcinoma)[1,6]

Study	DMH dose	Duration	Tumour incidence (%)	Main findings
Perse et al.	20 mg/kg	20 weeks	85	Adenocarcinoma formation
Bekusova et al.	21 mg/kg	20 weeks	100	Multiple colon tumors
Silva-Reis et al.	40 mg/kg	7 weeks	92	ACF and dysplasia
Wang et al.	40 mg/kg	10 weeks	88	CRC progression

Tumour Incidence Analysis

The overall success rate for colorectal tumour induction across the reviewed studies was notably high, ranging from 68% to 100%, depending on the specific protocol utilised.[1,6] Lesion severity progressed predictably over time, with early-stage markers like aberrant crypt foci appearing almost universally in treated animals.[1,2,6]

Table 2: Incidence of Colorectal Lesions Following DMH Exposure

Histopathological Findings-Aberrant crypt foci and hyperplastic crypts are the most frequent lesions (90–100% and 75–95%, respectively), indicating early and common preneoplastic changes after DMH exposure. Adenomas (60–90%) and adenocarcinomas (55–95%) occur less often but still frequently, reflecting progression from preneoplastic foci to benign and malignant tumours depending on dose and duration.

Lesion Type	Incidence Range (%)
Aberrant Crypt Foci (ACF)	90–100
Hyperplastic Crypts	75–95
Adenoma	60–90
Adenocarcinoma	55–95

DMH exposure catalysed a progressive cascade of pathological alterations, primarily localised to the distal colonic segments. Early signs included the formation of aberrant crypt foci and widespread goblet cell depletion, which subsequently advanced to severe crypt

distortion and mucosal dysplasia. In later stages, these cellular changes culminated in the development of distinct tubular adenomas and invasive adenocarcinomas.[1,2,5,6]

Molecular Mechanisms-The molecular profile of DMH-induced carcinogenesis heavily implicates oxidative stress, inflammatory signalling, and hyperproliferation.[1,2,4,8] DMH exposure consistently upregulated oxidative stress markers, drastically increasing malondialdehyde (MDA) and reactive oxygen species (ROS) levels, while simultaneously depleting the body's natural antioxidant defences, including superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH).[2,4] Inflammatory and proliferative pathways were similarly hyperactivated. Studies frequently noted the marked upregulation of inflammatory cytokines like TNF-α and IL-6, alongside overexpression of COX-2 and NF-Kb.[4,8] Additionally, markers of cellular proliferation—such as Ki-67, PCNA, and β-catenin—were highly expressed in tumour tissues[1,2,4]

Table 3: Major Molecular Alterations Observed.

Biomarker	**Expression status in tumor tissue**
β-Catenin	Increased
Ki-67	Increased
PCNA	Increased
TNF-α	Increased
IL-6	Increased
COX-2	Increased
MDA	Increased
SOD	Decreased

4. DISCUSSION

The DMH-induced colorectal carcinogenesis model remains one of the most thoroughly validated and reliable experimental systems for studying CRC.[1,6,9,10] The literature reviewed here demonstrates highly reproducible induction rates, frequently exceeding 80%, with several long-term studies reporting tumour development in nearly 100% of the animal subjects.[1,5] Crucially, the carcinogenic cascade in this model closely mirrors human colorectal tumorigenesis. The stepwise progression from aberrant crypt formation to adenoma and invasive carcinoma—coupled with the parallel activation of inflammatory networks, severe oxidative stress, and the dysregulation of Wnt/β-catenin signalling—provides a highly accurate biological proxy for the human disease3.[1,6-8] Because of its high incidence rates and predictable pathological evolution, this model is an exceptionally robust tool for evaluating a

wide array of interventions, including novel chemopreventive agents, phytochemicals, probiotics, targeted pharmaceuticals, and traditional Ayurvedic formulations.[4,6,9,10]

5. LIMITATIONS

While the DMH model is robust, this review identified several inconsistencies across the literature. Studies varied significantly in their DMH dosing schedules and total observation periods.[1,6] Furthermore, discrepancies in the histopathological grading systems utilised by different research teams, alongside a lack of standardised molecular biomarker panels, can make direct comparisons between studies challenging.[9,10]

6. CONCLUSION

The DMH-induced colorectal carcinogenesis model in albino Wistar rats delivers high tumour induction success rates and exhibits profound pathological similarity to human colorectal cancer.[1,6,9,10] The predictable, stepwise development of aberrant crypt foci, adenomas, and adenocarcinomas confirms its continued relevance as a gold-standard preclinical model.[1,6] It remains an indispensable resource for both understanding the fundamental biology of colorectal cancer and evaluating novel therapeutic strategies.[9,10]

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