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EXPERIMENTAL COLORECTAL CARCINOGENESIS IN ALBINO WISTAR RATS: INCIDENCE, TUMOUR BURDEN, AND INDUCTION SUCCESS RATE FOLLOWING 1,2-DIMETHYLHYDRAZINE EXPOSURE — NARRATIVE 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, Science Direct, 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 (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide, accounting for a substantial global health burden. According to recent epidemiological estimates, more than 1.9 million new cases and approximately 900,000 deaths are reported annually, with incidence rates continuing to rise in several developing countries due to rapid urbanisation, dietary transitions, obesity, physical inactivity, and ageing populations.[3,4] Despite significant advances in screening programmes, surgical techniques, chemotherapy, targeted therapies, and immunotherapy, colorectal cancer remains associated with considerable morbidity and mortality, particularly when diagnosed at advanced stages. The development of colorectal cancer is a multistep process involving the gradual transformation of normal colonic epithelium into invasive adenocarcinoma through the accumulation of genetic and epigenetic alterations. This progression follows the well-established adenoma–carcinoma sequence described by Fearon and Vogelstein, in which mutations affecting tumour suppressor genes, oncogenes, DNA repair pathways, and signalling cascades progressively drive neoplastic transformation.[5] Key molecular events include mutations in the adenomatous polyposis coli (APC) gene, activation of KRAS oncogenes, loss of TP53 function, microsatellite instability,

aberrant DNA methylation, and dysregulation of Wnt/β-catenin signalling pathways. These alterations result in uncontrolled cellular proliferation, resistance to apoptosis, angiogenesis, invasion, and eventual metastatic dissemination.[5,7,8] Given the complex and multifactorial nature of colorectal carcinogenesis, experimental animal models play a crucial role in understanding tumour biology, identifying molecular mechanisms, and evaluating preventive and therapeutic interventions. Animal models provide an opportunity to investigate disease progression under controlled conditions while reproducing many of the pathological and molecular characteristics observed in human colorectal cancer.[9,10] Over the past several decades, a variety of experimental models have been developed, including genetically engineered mouse models, xenograft models, orthotopic transplantation models, and chemically induced carcinogenesis models. Among these, chemically induced models remain particularly valuable because they closely mimic the sequential development of sporadic colorectal cancer in humans.[2,10]

Among the chemical carcinogens used for experimental induction of colorectal tumours, 1,2-dimethylhydrazine (DMH) has emerged as one of the most extensively utilised and validated agents. DMH is a potent colon-specific procarcinogen capable of inducing colorectal neoplasms that closely resemble human sporadic colorectal cancer in terms of histopathology, anatomical distribution, molecular alterations, and biological behaviour.[1,6] Following systemic administration, DMH undergoes metabolic activation in the liver through enzymatic oxidation pathways, producing intermediate metabolites such as azoxymethane (AOM) and methylazoxymethanol (MAM). These metabolites are subsequently converted into highly reactive methyl diazonium ions that interact with cellular DNA, resulting in methylation of nucleic acids, point mutations, chromosomal instability, and activation of oncogenic pathways.[1,6]

In addition to its direct genotoxic effects, DMH-induced carcinogenesis is strongly associated with oxidative stress and chronic inflammation. Metabolic activation of DMH generates reactive oxygen species (ROS), which promote lipid peroxidation, mitochondrial dysfunction, DNA damage, and activation of pro-inflammatory mediators. The resulting inflammatory microenvironment contributes significantly to tumour initiation, promotion, and progression.[8,9] Consequently, DMH-induced colorectal carcinogenesis closely recapitulates the interaction between genetic instability, oxidative stress, and inflammation that characterises human colorectal cancer. The pathological progression observed following

DMH administration follows a sequence remarkably similar to human colorectal tumour development. The earliest detectable lesions are aberrant crypt foci (ACF), first described by Bird as putative preneoplastic markers of colorectal carcinogenesis.[12] These lesions subsequently progress to dysplastic crypts, adenomatous polyps, and ultimately invasive adenocarcinomas through a series of morphological and molecular changes. Histologically, DMH-induced tumours exhibit epithelial dysplasia, glandular distortion, crypt branching, inflammatory infiltration, mucosal ulceration, and adenocarcinoma formation, thereby reproducing the adenoma–carcinoma sequence characteristic of human colorectal cancer.[5,7,12]

Albino Wistar rats have become one of the most widely employed experimental species for DMH-induced colorectal carcinogenesis owing to their favourable biological characteristics, including susceptibility to colon-specific tumour induction, ease of handling, well-characterised physiology, and reproducible tumour development. Numerous studies have demonstrated that repeated DMH administration in Wistar rats results in high tumour induction rates, predictable tumour localisation within the distal colon, and reproducible histopathological progression. These features have established the DMH-Wistar rat model as a valuable platform for investigating carcinogenic mechanisms and assessing the efficacy of chemopreventive agents, phytochemicals, dietary interventions, conventional anticancer drugs, and Ayurvedic formulations.[1,13,15] Although DMH-induced colorectal carcinogenesis has been extensively utilised in experimental oncology research, substantial variability exists among published studies regarding carcinogen dosage, route of administration, treatment duration, induction success rates, tumour multiplicity, mortality, and histopathological outcomes. Such heterogeneity often complicates direct comparison between studies and limits the standardisation of experimental protocols. Furthermore, while numerous investigations have reported tumour incidence and pathological findings, a comprehensive synthesis of these outcomes remains limited. Therefore, the present systematic review was undertaken to critically evaluate the available evidence on DMH-induced colorectal carcinogenesis in albino Wistar rats. Specifically, this review aims to analyse tumour incidence rates, tumour burden, induction success, mortality during carcinogen exposure, and histopathological outcomes reported across published studies. By consolidating existing evidence, the review seeks to provide a comprehensive overview of the reliability, reproducibility, and translational relevance of the DMH-Wistar rat model and to support its continued application in colorectal cancer research and preclinical drug evaluation.

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, Science Direct, 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
- studies included in qualitative synthesis: n = 36
- Final studies included in qualitative synthesis n=10

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 tumour 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]

Table: Comparison of Findings from the Present Systematic Review with Published Literature on DMH-Induced Colorectal Carcinogenesis.

Parameter	Findings of the Present Systematic Review	Findings from Previous Literature	Interpretation
Tumour induction success	High induction success observed across most included studies, demonstrating reliable colorectal tumour formation in Wistar rats.	DMH consistently induces colorectal tumours with induction rates often exceeding 70–90% depending on dose and duration (Perše & Cerar, 2011; Newell & Heddle, 2004).[1,6]	Confirms the reproducibility and reliability of DMH as a colon-specific carcinogen.
Tumour incidence	Majority of animals developed colorectal neoplasms following repeated DMH administration.	Similar high tumour incidence has been reported in chemically induced CRC models using DMH and AOM (Perše & Cerar, 2011; Corpet & Pierre, 2005).[1,14]	Supports the utility of the model for evaluating anticancer interventions.
Tumour burden (Multiplicity)	Increased tumour number with prolonged exposure and cumulative dose.	Tumour multiplicity is dose-dependent and increases with longer carcinogen exposure periods (Bird, 1987; Tanaka, 2012).[12,13]	Indicates a clear relationship between carcinogen exposure and tumour progression.
Anatomical tumour location	Tumours predominantly developed in distal colon and rectum.	Human CRC and DMH-induced tumours both preferentially occur in the distal colon (Perše & Cerar, 2011).[15]	Enhances translational relevance of the model.
Early pathological lesions	Aberrant crypt foci (ACF) were consistently reported as initial lesions.	ACF are recognised as the earliest preneoplastic biomarkers of colorectal carcinogenesis (Bird, 1987).[12]	Demonstrates that DMH reproduces the earliest stages of colorectal cancer development.

Histopathological progression	Sequential progression from ACF → adenoma → adenocarcinoma was observed.	The adenoma–carcinoma sequence is a hallmark of both human CRC and DMH-induced carcinogenesis (Fearon & Vogelstein, 1990; Leslie et al., 2002).[5,7]	Confirms close pathological resemblance to human colorectal cancer.
Molecular mechanisms	DNA alkylation, oxidative stress, inflammation, and mutagenesis were key pathogenic events.	DMH metabolites induce DNA methylation, ROS generation, and chronic inflammatory responses (Newell & Heddle, 2004; Mármol et al., 2017).[6,8]	Indicates mechanistic similarity to human colorectal carcinogenesis.
Inflammatory changes	Inflammatory infiltrates, mucosal ulceration, and crypt abscesses were frequently reported.	Chronic inflammation is a recognised driver of tumour initiation and progression in CRC (West et al., 2015).[9]	Supports the role of inflammation in DMH-induced tumour development.
Mortality during induction	Low-to-moderate mortality with most animals surviving the experimental period.	Previous studies report acceptable survival rates despite long-term carcinogen exposure (Perše & Cerar, 2011).[15]	Demonstrates feasibility for long-duration chemoprevention studies.
Suitability for therapeutic evaluation	Model successfully reproduced progressive tumour development suitable for testing interventions.	Widely used for evaluating chemopreventive agents, phytochemicals, and novel therapeutics (Corpet & Pierre, 2005; Tanaka, 2012).[13,14]	Supports continued use in preclinical drug and Ayurveda research.
Limitations	Variability in dose, duration, and outcome reporting among studies.	Similar methodological heterogeneity has been reported in previous systematic assessments (Corpet & Pierre, 2005).[14]	Highlights need for protocol standardisation and reporting guidelines.
Overall translational relevance	DMH-Wistar model closely mimics human sporadic colorectal carcinogenesis.	Considered one of the most clinically relevant chemically induced CRC models (Perše & Cerar, 2011; Rosenberg et al., 2009).[2,15]	Validates its role in translational colorectal cancer research.

ACF: Aberrant Crypt Foci; CRC: Colorectal Cancer; DMH: 1,2-Dimethylhydrazine

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.

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

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.

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 present systematic review evaluated the incidence, tumour burden, induction success rate, and pathological outcomes associated with 1,2-dimethylhydrazine (DMH)-induced colorectal carcinogenesis in albino Wistar rats. The findings demonstrate that DMH consistently produces colorectal neoplasms with high induction success rates and pathological features closely resembling human sporadic colorectal cancer, reinforcing its value as a reliable experimental model for colorectal cancer research. A major observation of this review is the consistently high tumour induction rate reported across the included studies. Most investigations employing repeated DMH administration successfully induced colorectal tumours in a substantial proportion of animals, confirming the potent carcinogenic potential of DMH. These findings are in agreement with previous reports indicating that DMH exhibits remarkable colon specificity and reproducibly induces premalignant and malignant lesions in rodents through metabolic activation and DNA methylation mechanisms. Following hepatic conversion to methylazoxymethanol and subsequent formation of methyl diazonium ions, DMH generates DNA adducts and mutagenic lesions that initiate colorectal carcinogenesis through pathways analogous to those observed in human disease.[1,6] The tumour burden observed across studies further supports the effectiveness of the DMH model. Multiple investigations reported the development of numerous tumours per animal, particularly in the distal colon and rectum, reflecting the anatomical distribution frequently observed in human colorectal cancer. Tumour multiplicity increased with prolonged exposure duration and cumulative carcinogen dose, suggesting a dose-dependent carcinogenic response. Similar observations have been documented in experimental studies demonstrating that repeated DMH administration promotes progressive epithelial transformation, resulting in increased tumour incidence and multiplicity over time.[12,13]

Histopathological evaluation revealed a characteristic progression from aberrant crypt foci (ACF) to adenomas and ultimately invasive adenocarcinomas. Aberrant crypt foci are widely recognised as the earliest detectable preneoplastic lesions in chemically induced colorectal carcinogenesis and serve as important biomarkers for tumour development. The sequential appearance of dysplastic crypts, glandular distortion, epithelial hyperplasia, and adenocarcinoma observed in the reviewed studies closely mirrors the adenoma–carcinoma sequence described in human colorectal cancer. This resemblance strengthens the

translational relevance of the DMH model and supports its continued use in mechanistic and therapeutic investigations.[5,7] The pathological findings identified in this review also highlight the multifactorial nature of DMH-induced carcinogenesis. In addition to direct genotoxicity, DMH-generated reactive oxygen species contribute substantially to oxidative stress, lipid peroxidation, chronic inflammation, and cellular injury. These processes collectively create a pro-tumorigenic microenvironment that facilitates tumour initiation and progression. Several studies reported inflammatory infiltration, mucosal ulceration, crypt abscesses, and increased oxidative damage markers within tumour-bearing tissues, suggesting that inflammation and oxidative stress are critical mediators of DMH-induced tumour development. These observations are consistent with current understanding of colorectal carcinogenesis, in which chronic inflammation and oxidative injury contribute significantly to malignant transformation.[8,9] An important finding of this review is the relatively low mortality reported during carcinogen induction in most studies. Although occasional animal deaths were observed, particularly with higher doses or prolonged treatment schedules, the overall survival rates remained adequate for experimental purposes. This favourable balance between tumour induction efficiency and animal survival enhances the practicality of the DMH-Wistar rat model for long-term studies evaluating chemopreventive and therapeutic interventions. Similar conclusions have been reported by Perše and Cerar, who emphasised the reproducibility and feasibility of this model for colorectal cancer research.[15] Despite its advantages, certain limitations of the DMH model were evident from the reviewed literature. Considerable variability existed among studies regarding DMH dosage, route of administration, duration of exposure, observation period, and outcome assessment methods. Such methodological heterogeneity may influence tumour incidence, latency, and histopathological severity, thereby limiting direct comparison between studies. Furthermore, while DMH-induced tumours closely resemble human sporadic colorectal cancer morphologically, the model does not fully replicate the complex genetic diversity, tumour microenvironment, and metastatic behaviour observed in clinical settings. Therefore, findings derived from this model should be interpreted alongside evidence from complementary experimental systems, including genetically engineered mouse models and xenograft models.[2,10] Nevertheless, the evidence synthesised in this review strongly supports the continued application of DMH-induced colorectal carcinogenesis in albino Wistar rats as a robust and translationally relevant experimental model. The model reliably reproduces key stages of colorectal tumour development, including aberrant crypt formation, adenoma progression, and adenocarcinoma formation, while maintaining acceptable survival rates and

reproducibility. These characteristics make it particularly valuable for investigating molecular mechanisms of colorectal carcinogenesis and evaluating novel pharmacological, dietary, and Ayurvedic interventions aimed at cancer prevention and treatment. The findings of this systematic review indicate that DMH-induced colorectal carcinogenesis in albino Wistar rats remains one of the most reliable and widely accepted experimental models for studying colorectal cancer. High tumour induction rates, significant tumour burden, reproducible histopathological progression, and close resemblance to human colorectal carcinogenesis collectively support its utility in preclinical oncology research. Standardisation of experimental protocols and reporting practices may further enhance the comparability and translational value of future studies employing this model.

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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