Therapeutic Efficacy of Sunitinib in NMU-Induced Mammary Carcinogenesis in Rats

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Abstract

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, necessitating the development of effective therapeutic strategies. This study aimed to evaluate the antitumour efficacy of sunitinib in an N-methyl-N-nitrosourea (NMU)-induced rat model of mammary carcinogenesis.

Eighteen female Sprague–Dawley rats were administered NMU (70 mg/kg, intraperitoneally) to induce mammary tumours. Tumour development was monitored through palpation and caliper measurements. Upon reaching a mean tumour size of 14 ± 0.5 mm, animals received intralesional sunitinib treatment, while control animals received normal saline. Tumour size, incidence, body weight, and histopathological changes were evaluated.

NMU successfully induced mammary tumours in 94.44% of rats, with a mean tumour multiplicity of 1.67 ± 0.91 tumours per animal. Sunitinib treatment resulted in a reduction in tumour diameter from 15.13 ± 1.33 mm to 12.98 ± 2.48 mm, whereas tumour growth increased in the control group. No significant differences in body weight were observed between groups ($P > 0.05$), indicating minimal systemic toxicity. Histological analysis revealed predominantly cribriform carcinomas, with no major alterations in tumour architecture following treatment.

In conclusion, sunitinib effectively suppresses tumour progression in NMU-induced mammary tumours without inducing significant toxicity, highlighting its potential as a targeted anti-angiogenic therapy for breast cancer. Further studies are warranted to explore its molecular mechanisms and long-term therapeutic efficacy.

Keywords: Breast cancer; Sunitinib; NMU-induced model; Mammary tumours; Angiogenesis inhibition; Tyrosine kinase inhibitor; Sprague–Dawley rats

Introduction

Breast cancer (BC) remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide (Zoroddu et al., 2024). According to recent global estimates, approximately 2.3 million new cases and 670,000 deaths were recorded in 2024 alone

(World Health Organization, 2024). Despite notable progress in early detection strategies and therapeutic interventions, breast cancer continues to pose a substantial global health burden, with both incidence and mortality rates expected to increase in the coming decades (Liu et al., 2025).

Preclinical animal models, particularly rat models, have become indispensable tools for elucidating the molecular mechanisms underlying breast cancer initiation, progression, and metastasis, as well as for evaluating novel therapeutic strategies (Liu et al., 2021). Rodents are widely utilized due to their close biological resemblance to human breast cancer in terms of epithelial origin, hormonal dependence, gene expression profiles, and mammary gland architecture (Liu et al., 2021; Nicotra et al., 2024). Among these, female Sprague–Dawley (SD) rats are considered one of the most reliable models for studying chemically induced mammary carcinogenesis. Specifically, N-methyl-N-nitrosourea (NMU)-induced tumours in SD rats closely resemble human breast cancer, as they are estrogen-dependent, originate from ductal epithelial cells, and exhibit responsiveness to anti-estrogen therapies (Yankuzo et al., 2014). Furthermore, this model replicates the multistep process of carcinogenesis—including initiation, promotion, and progression—thereby providing a robust platform for investigating tumour biology and therapeutic responses (Silva et al., 2023). The high reproducibility of tumour induction following NMU administration further enhances its utility in controlled experimental studies (Gao et al., 2021).

Chemical carcinogen-induced models are extensively employed in breast cancer research due to their ability to mimic environmentally driven carcinogenesis. These models enable the investigation of cancer-related mechanisms, including genetic and epigenetic alterations, tumour microenvironment dynamics, angiogenesis, and immune responses (Y. Liu et al., 2015; Sewduth & Georgelou, 2024). Several chemical agents have been used for tumour induction, such as N-methyl-N-nitrosourea (NMU), 7,12-dimethylbenzanthracene (DMBA), methylcholanthrene (MCA), diethylnitrosamine (DEN), and azoxymethane (AOM) (Sharma et al., 2021). Among these, NMU and DMBA are the most commonly employed carcinogens, administered via intravenous, intraperitoneal, or intragastric routes (Silva et al., 2025). Notably, NMU is widely recognized for its potent carcinogenic properties and its ability to induce mammary tumours that closely resemble human breast cancer, making it an ideal model for screening anticancer agents (Gao et al., 2021; Tsubura et al., 2011).

In parallel with advances in conventional therapies, there has been increasing interest in the development of novel targeted and adjunctive treatments to overcome therapeutic resistance, a major challenge in cancer management (Gal et al., 2020). One such promising agent is sunitinib, a multi-target receptor tyrosine kinase (RTK) inhibitor that exerts its effects by targeting key signalling pathways involved in tumour angiogenesis and growth, including vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3) and platelet-derived growth factor receptors (PDGFR) (Qian & Yi, 2025; Wang et al., 2020). Hallmarks of cancer, such as sustained proliferative signalling, resistance to apoptosis, and enhanced angiogenesis, contribute to tumour progression and therapeutic failure (Zulkefly et al., 2023). By targeting these critical pathways, sunitinib has emerged as a potential therapeutic candidate for breast cancer treatment.

Materials and Methods

Animal Handling and Ethical Approval

Eighteen female Sprague–Dawley rats (20 days old) were obtained from the Animal Research and Service Centre (ARASC), Universiti Sains Malaysia (USM). Animals were housed in polycarbonate cages (three rats per cage) containing wood chip bedding under controlled environmental conditions (temperature: 24 °C; 12 h light/12 h dark cycle). Standard laboratory chow and tap water were provided ad libitum throughout the experimental period.

All experimental procedures involving animals were conducted in strict compliance with the guidelines for the care and use of laboratory animals approved by ARASC, USM, and were performed under institutional ethical approval (USM/IACUC/2020/(122)(1052)). Animal welfare was monitored continuously under the supervision of ARASC husbandry staff.

Tumour Induction and Monitoring

N-methyl-N-nitrosourea (NMU) was purchased from Oakwood Chemicals (USA) and freshly prepared prior to administration. The compound was dissolved in 0.9% normal saline by gentle heating in a water bath, followed by vigorous mixing to ensure complete dissolution.

NMU was administered intraperitoneally (IP) at a dose of 70 mg/kg body weight on two occasions at alternate-day intervals. Prior to injection, animals were anaesthetized using a ketamine–xylazine combination.

Following NMU administration, rats were weighed every alternate day and examined twice weekly by palpation for the detection of mammary tumours. Tumour development was monitored by measuring lesion diameters using a vernier caliper. In addition, animals were closely observed for any signs of toxicity or adverse effects associated with NMU exposure.

Sunitinib Treatment Protocol

Tumour growth was monitored until lesions reached an average diameter of 14 ± 0.5 mm, at which point treatment was initiated. Sunitinib was prepared in 0.9% normal saline to obtain a final concentration of 5 mg/0.2 mL (total volume: 1 mL).

The treatment group received intralesional injections of sunitinib twice on alternate days, whereas the control (vehicle) group received equivalent volumes of normal saline. Tumour response was monitored for one week following treatment administration. At the end of the experimental period, animals were sacrificed for further analysis.

Tumour dimensions were measured using a vernier caliper and recorded for subsequent evaluation.

Tumour Sample Collection and Histopathological Analysis

All animals were euthanized by exsanguination under ketamine–xylazine anaesthesia. During necropsy, all visible mammary tumours, normal mammary tissue, and relevant organs were excised. Each tumour sample was divided into two portions: one portion was fixed in 10% neutral buffered formalin at room temperature for 24 hours to ensure optimal tissue preservation for histological analysis, while the other portion was preserved in RNAlater solution for potential molecular studies. Formalin-fixed tissues were processed, embedded in paraffin, and sectioned. Tissue sections were subsequently deparaffinized, rehydrated using xylene and graded ethanol, and stained with hematoxylin and eosin (H&E) for histopathological evaluation.

Results and Discussion

Tumour Incidence and Latency

Histopathological and macroscopic evaluations demonstrated a high tumour induction efficiency in the NMU model, with an overall mammary tumour incidence of **94.44% (17/18 rats)**, yielding a total

of **30 tumours**. The tumour multiplicity ranged from 0 to 3 tumours per rat, with a mean of **1.67 ± 0.91 tumours per animal**, indicating a consistent and reproducible carcinogenic response.

The first palpable tumours were detected at **8 weeks post-second NMU administration** in 16.67% of animals, while the majority of tumours (55.55%) developed between **weeks 9 and 16**, reflecting a progressive and time-dependent tumour emergence. By the end of the experimental period, tumour incidence increased markedly, reaching **93.7% of animals**, confirming the robustness of the NMU-induced mammary carcinogenesis model.

Interestingly, tumour incidence was slightly higher in the sunitinib-treated group (**100%**) compared to the control group (**88.89%**). This observation suggests that sunitinib administration did not interfere with tumour initiation, which is consistent with its known mechanism as a **post-initiation therapeutic agent targeting tumour progression and angiogenesis rather than carcinogenic induction**.

Overall, the latency period and high tumour incidence observed in this study are in agreement with previous reports demonstrating that NMU induces **rapid-onset, hormone-dependent mammary tumours** that closely resemble human breast cancer, thereby validating the suitability of this model for therapeutic evaluation.

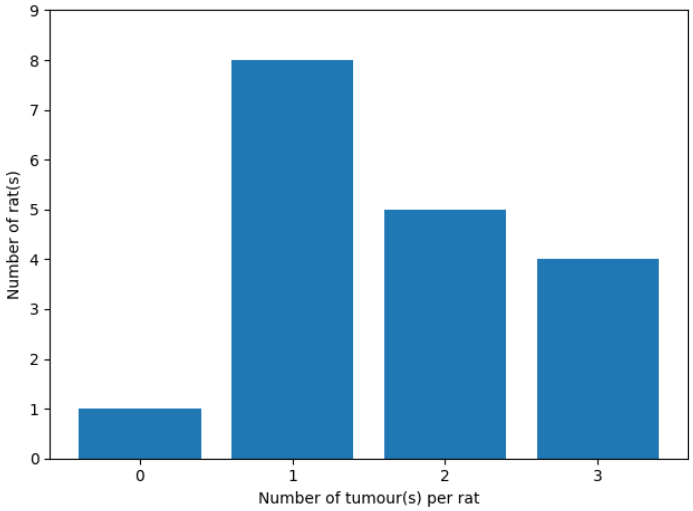

Figure 1: The Frequency of mammary tumours in NMU-induced rats

Tumour Growth Dynamics and Response to Sunitinib

A marked divergence in tumour growth patterns was observed between the sunitinib-treated and control groups. In the treated group, tumour diameter significantly decreased from **15.13 ± 1.33 mm** (pre-treatment) to **12.98 ± 2.48 mm** after seven days, indicating a clear tumour regression. In contrast, tumours in the control group exhibited continuous growth, increasing from **15.69 ± 3.64 mm** to **19.76 ± 5.54 mm** over the same period.

These findings demonstrate that sunitinib exerts a **significant inhibitory effect on tumour growth**, likely mediated through its anti-angiogenic activity via inhibition of VEGFR and PDGFR signalling pathways. By disrupting tumour vascularization, sunitinib may reduce nutrient and oxygen supply, thereby limiting tumour expansion.

The rapid response observed within a short treatment duration (7 days) further highlights the **potent pharmacological activity of sunitinib in established tumours**, supporting its potential as a targeted therapeutic agent in breast cancer management.

Body Weight Changes and Systemic Toxicity

Body weight analysis revealed no statistically significant differences between the sunitinib-treated and control groups (**P > 0.05**), indicating that sunitinib administration did not induce noticeable systemic toxicity over the treatment period. Both groups maintained relatively stable body weights, suggesting that the observed antitumour effects were not associated with general health deterioration or cachexia.

This finding is particularly important, as it supports the **favourable tolerability profile of sunitinib at the administered dose**, reinforcing its suitability for further preclinical and translational investigations.

Table 1: Tumour diameter (mean ± SD) of the Sunitinib-treated and control groups before first treatment and after seven days of second treatment

Group	**Before First Treatment (mm)**	**7 Days After Second Treatment (mm)**
Sunitinib-treated	15.13 ± 1.33	12.98 ± 2.48
Control	15.69 ± 3.64	19.76 ± 5.54

Body Weight Changes and Systemic Toxicity

Body weight analysis revealed no statistically significant differences between the sunitinib-treated and control groups ($P > 0.05$), indicating that sunitinib administration did not induce measurable systemic toxicity during the treatment period. Both groups maintained relatively stable body weights throughout the study, suggesting that the observed antitumour effects were not accompanied by general health deterioration, metabolic imbalance, or cancer-associated cachexia.

Body weight is widely recognized as a sensitive and integrative indicator of systemic toxicity in preclinical oncology studies, reflecting the overall physiological and metabolic status of experimental animals (Bailey et al., 2014). In this context, the absence of significant weight loss in the sunitinib-treated group supports the notion that the administered dose was well tolerated. This observation is particularly relevant given that many conventional chemotherapeutic agents are commonly associated with adverse systemic effects, including anorexia, gastrointestinal toxicity, and progressive weight loss (Argilés et al., 2014).

The favourable tolerability profile observed in this study is consistent with previous reports on sunitinib, which demonstrate that its targeted mechanism of action—primarily through inhibition of VEGFR and PDGFR signalling—results in reduced off-target cytotoxicity compared to traditional chemotherapy (Motzer et al., 2006; Faivre et al., 2007). Unlike cytotoxic agents that directly damage rapidly dividing normal cells, sunitinib selectively disrupts tumour angiogenesis and stromal support, thereby limiting tumour progression while preserving systemic homeostasis.

Moreover, the maintenance of body weight may reflect the preservation of normal metabolic and nutritional status, suggesting that sunitinib did not significantly impair feeding behaviour or induce severe organ toxicity within the short treatment duration. This aligns with findings from preclinical and clinical studies indicating that short-term administration of tyrosine kinase inhibitors is generally associated with manageable toxicity profiles, particularly when administered at optimized doses (Chow & Eckhardt, 2007).

Importantly, the absence of cachexia in the treated group also implies that tumour burden reduction was not achieved at the expense of host tissue wasting. Cancer-associated cachexia is a multifactorial syndrome driven by systemic inflammation, metabolic dysregulation, and tumour-host interactions, and is often exacerbated by aggressive treatments (Argilés et al., 2014). Therefore, the ability of sunitinib to suppress tumour growth without inducing weight loss further highlights its therapeutic advantage.

However, it should be noted that the duration of this study was relatively short (7 days post-treatment), which may limit the detection of delayed or cumulative toxic effects. Previous studies have reported that prolonged exposure to sunitinib can be associated with adverse effects such as hepatotoxicity, hypertension, and fatigue (Faivre et al., 2007). Therefore, extended-duration studies incorporating biochemical, hematological, and organ-specific toxicity assessments are warranted to comprehensively evaluate the safety profile of sunitinib in this model.

Overall, these findings support the **favourable safety and tolerability profile of sunitinib**, reinforcing its potential as a targeted therapeutic agent in breast cancer. The combination of effective tumour suppression and minimal systemic toxicity underscores its relevance for further preclinical validation and potential translational application.

Table 2: Body Weight changes in control and suntinib-treated groups

Data are mean±SEM.; *P>0.05 compared to control (unpaired, two-tailed t-test)

Group	**Initial Body Weight (g)**	**Final Body Weight (g)**	**Percentage Change (%)**
Control	274.63 ± 9.71	273.88 ± 18.31	54.25
Sunitinib-treated	270.90 ± 18.31*	269.67 ± 22.81*	52.94

Histopathological Characteristics

Histological analysis identified 30 mammary tumours, predominantly classified as cribriform invasive breast carcinoma (80%), with the remaining 20% exhibiting papillary carcinoma morphology. The cribriform subtype, which is generally considered less aggressive, was the most prevalent in both groups—accounting for 71.43% in the control group and 87.50% in the sunitinib-treated group.

The predominance of cribriform carcinoma suggests that NMU preferentially induces moderately differentiated tumour phenotypes, consistent with previous reports describing NMU-induced tumours as hormonally responsive and structurally comparable to human luminal-type breast cancers.

Importantly, no major shift in tumour histological subtype distribution was observed between treated and control groups, indicating that while sunitinib effectively suppressed tumour growth, it did not significantly alter tumour differentiation patterns within the experimental timeframe.

However, the higher proportion of cribriform tumours in the treated group may suggest a potential selective inhibitory effect on more aggressive tumour phenotypes, although this observation requires further investigation through extended treatment durations and molecular characterization.

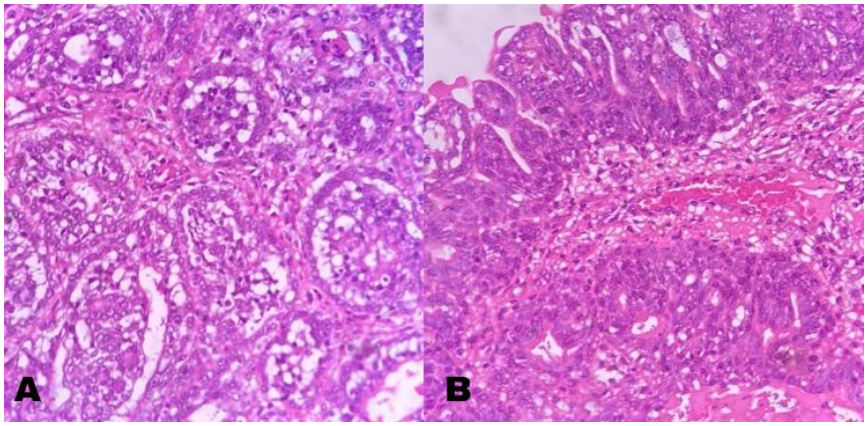

Figure 2. A: NMU-induced invasive carcinoma of cribriform. B: NMU-induced invasive carcinoma of papillary

Overall Interpretation

Collectively, the findings of this study demonstrate that NMU is a highly effective carcinogen for inducing mammary tumours with high incidence and predictable latency, thereby confirming the robustness and translational relevance of this model in breast cancer research. The rapid tumour onset and high penetrance observed are consistent with previous reports indicating that NMU-induced mammary tumours closely resemble human hormone-dependent breast cancers in both histopathological and biological characteristics (Tsubura et al., 2011; Gao et al., 2021).

Importantly, the present data indicate that sunitinib exerts a pronounced inhibitory effect on tumour progression rather than tumour initiation, as evidenced by the lack of impact on tumour incidence alongside significant tumour regression following treatment. This distinction is critical and aligns with the pharmacological profile of sunitinib as a multi-target receptor tyrosine kinase inhibitor, primarily acting on angiogenic and stromal pathways rather than directly preventing carcinogenic transformation (Qian & Yi, 2025; Wang et al., 2020).

The observed reduction in tumour size in the treated group strongly suggests that sunitinib effectively disrupts tumour growth dynamics, most likely through inhibition of VEGFR- and PDGFR-mediated signalling pathways, which play central roles in tumour angiogenesis, vascular permeability, and stromal support (Motzer et al., 2006; Faivre et al., 2007). Angiogenesis is a fundamental hallmark of cancer, enabling tumour expansion beyond a critical size by ɯɥɯhnɻing oxygen and nutrient supply

(Hanahan & Weinberg, 2011). Therefore, the anti-angiogenic action of sunitinib likely results in reduced vascularization, hypoxia induction, and subsequent suppression of tumour growth.

In addition to its anti-angiogenic effects, sunitinib may also contribute to tumour control by modulating the tumour microenvironment, including inhibition of pericyte recruitment and interference with tumour–stromal interactions. Emerging evidence suggests that tyrosine kinase inhibitors can alter immune cell infiltration and reduce pro-tumorigenic signalling within the tumour niche, thereby enhancing therapeutic efficacy (Chow & Eckhardt, 2007). This multifaceted mechanism may explain the rapid tumour regression observed within a relatively short treatment duration in the present study.

Equally important is the absence of significant systemic toxicity, as reflected by stable body weight in the treated animals. This finding is consistent with previous studies demonstrating that targeted therapies such as sunitinib exhibit a more favourable safety profile compared to conventional chemotherapeutic agents, which are often associated with severe systemic side effects and weight loss (Argilés et al., 2014; Faivre et al., 2007). The ability of sunitinib to suppress tumour growth without inducing cachexia or general physiological deterioration underscores its therapeutic advantage and potential for clinical translation.

Furthermore, the preservation of histological architecture and the predominance of less aggressive tumour subtypes suggest that while sunitinib effectively limits tumour expansion, it does not induce adverse morphological alterations within the short experimental timeframe. This observation may indicate a cytostatic rather than cytotoxic mode of action, which is characteristic of many anti-angiogenic therapies.

Despite these promising findings, several limitations should be acknowledged. The relatively short duration of treatment (7 days) may not fully capture long-term therapeutic outcomes or delayed toxic effects. Additionally, the absence of molecular analyses—such as expression levels of angiogenic markers (e.g., VEGF, CD31) or apoptosis-related proteins—limits the mechanistic interpretation of the observed effects. Future studies should incorporate extended treatment durations, dose-response evaluations, and molecular profiling to further elucidate the pathways underlying sunitinib-mediated tumour suppression.

Overall, the results of this study are consistent with the growing body of evidence supporting the role of targeted tyrosine kinase inhibitors in regulating tumour angiogenesis and microenvironmental interactions, thereby suppressing cancer progression. These findings provide a strong experimental foundation for further mechanistic investigations and support the potential application of sunitinib as a therapeutic strategy in breast cancer, particularly in angiogenesis-driven tumour subtypes.

Conclusion

In conclusion, the present study demonstrates that N-methyl-N-nitrosourea (NMU) effectively induces mammary tumours in Sprague–Dawley rats with high incidence and predictable latency, confirming its suitability as a reliable preclinical model for breast cancer research.

Sunitinib treatment resulted in a significant reduction in tumour size without affecting tumour incidence, indicating that its primary effect is on tumour progression rather than initiation. This antitumour activity is likely mediated through inhibition of angiogenic signalling pathways,

particularly VEGFR and PDGFR, leading to impaired tumour vascularization and growth suppression.

Importantly, the absence of significant body weight changes suggests that sunitinib was well tolerated and did not induce noticeable systemic toxicity during the treatment period. Additionally, histopathological findings revealed preservation of tumour architecture, supporting a cytostatic mode of action.

Overall, these findings highlight the potential of sunitinib as an effective anti-angiogenic therapeutic agent in breast cancer. However, further studies incorporating longer treatment durations, molecular analyses, and dose optimization are required to fully elucidate its mechanisms of action and to support its translational application in clinical settings.

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