RESEARCH PAPER

Protective Role of *Asparagus racemosus* Against NMU + Cisplatin-Induced Hematological and Histopathological Alterations in a Rat Model of Triple-Negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer that lacks estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, resulting in a poor prognosis and limited treatment options. In experimental oncology, N-methyl-N-nitrosourea (NMU) is commonly used to induce mammary cancer in rodents, whereas cisplatin remains a first-line chemotherapy agent due to its serious systemic side effects such as anemia, leukopenia, and tissue destruction. The purpose of this study is to investigate the protective effect of the extract of *Asparagus racemosus* against hematological and histological changes caused by NMU + cisplatin in Wistar rats.

Four groups of healthy female rats were formed according to the following treatments: control group; NMU + cisplatin; NMU + *Asparagus racemosus* 500 mg/kg; and NMU + *Asparagus racemosus* 1000 mg/kg. Blood parameters (RBCs, Hb, PCV, WBCs, platelets, etc.) were determined and mammary tissues analyzed histologically. Treatment with NMU + cisplatin showed a significant decrease in RBCs, Hb, PCV, WBCs, and the number of platelets, indicating the presence of bone marrow depression and toxicity. Histopathological analysis revealed loss of ductal structure, mucus deposition, and proliferation of fibrous tissue.

Treatment with *A. racemosus* showed dose-dependent effect. 500 mg/kg dosage showed incomplete recovery of blood parameters and structure of mammary tissues; however, with dosage of 1000 mg/kg analyzed parameters returned to normal and ductal structure got almost completely restored. These results indicate that *A. racemosus* has protective effects against NMU + cisplatin toxicity due to its antioxidant, anti-inflammatory and immunomodulatory properties. The relationship between blood recovery and improvement in histopathology highlights the systemic and local effectiveness of *A. racemosus*. It makes *A. racemosus* a promising candidate for use in TNBC treatment, decreasing chemotoxicity and aiding in tissue recovery. Further molecular and clinical studies can confirm its therapeutic effectiveness.

Keywords: Triple-negative breast cancer; N-methyl-N-nitrosourea; Cisplatin; *Asparagus racemosus*; Hematological parameters; Histopathology; Chemotoxicity; Adjunct therapy

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INTRODUCTION:

NMU-Induced Carcinogenesis and Cisplatin Toxicity:

Breast cancer is one of the most common forms of malignancy across the world, causing serious morbidity and mortality in women as a result of cancer. The subtype known as triple-negative breast cancer (TNBC) is among the most aggressive forms of the disease with a contribution level of around 15-20% of cases diagnosed as breast cancer [1],[2],[3],[4],[5].

TNBC is characterized by the lack of estrogen receptors (ER), progesterone receptor (PR), and human epidermal growth factor receptor2 (HER2), which creates resistance to conventional hormonal and targeted therapeutic methods. This subtype is characterized by a poor prognosis, high recurrence rate, and a lack of treatment options making it a vital target for the invention of novel preventive and therapy-related methods [6],[7],[8],[9],[10],[11].

Laboratory models have played an important role in elucidating the biology of TNBC. For initiation of mammary gland tumor formation in rodent experiments, N-methyl-N-nitrosourea (NMU) has been used as a powerful carcinogen [11].[12],[13],[14],[15],[16]. NMU serves as a potent carcinogen by alkylating DNA resulting in mutations in important tumor suppressor and oncogenes which facilitates tumor formation. The NMU-based model involving rats has been proven to demonstrate certain molecular properties and mechanisms similar to that of TNBC in humans, allowing for proper evaluations of the different anticancer medicines [17],[18],[19],[20],[21],[22].

Cisplatin is an antineoplastic drug used in chemotherapy in the most aggressive cases when dealing with tumors like breast cancer. The mechanism of action of cisplatin triggers the formation of the significant DNA adducts within tumor cells leading to their apoptosis [23],[24],[25]. However, it should be noted that the effectiveness of the drug goes hand in hand with numerous side effects that include nephro- and hepatotoxicity as well as neurotoxic and myelosuppressive effects of the drug. Studies carry out on the animal models of cancer development have shown that the methods mentioned above are associated with increased toxicity. The studies indicate the presence of relationships among cisplatin, leukemia, anemia, and tissue destruction. Thus, animal models of the carcinogenicity induced by NMU and the toxicity of cisplatin can provide a good preclinical model simulating the condition of cancer patients [26].[27],[28],[29],[30].

Importance of Hematological and Histopathological Markers:

Hematological study DNA plays an important role in ascertaining the systemic toxicity and effectiveness of different treatments in oncology research. Samples are taken from the blood mentioning their RBC counts, HB content, PCV, WBC level, and number of platelets [31],[32],[33],[34],[35]. In NMU+Cisplatin experiments, significant decrease in RBC content, amount of HB, and PCV level indicates that the body suffers from anemia, while low WBC amount implies leukopenia and suppression of immunity. Decrease of platelets may serve as a confirmation that haematopoysis is disturbed and the risk of bleeding is increased. Therefore, the improvement of these indices is regarded as evidence of the renewed bone marrow activity and confirmed systemic safety [36],[37],[38],[39]. Histopathological study also contributes to understanding the processes taking place in the tissues. For instance, in the case of mammary cells, NMU-induced malignancy can be detected by the lack of tissue structure as well as disordered production of ducts and mucins and growing amount of connective tissue elements. Also, Cisplatin treatment contributes to the appearance of even greater tissue disturbances. On the contrary, effective agents with protective features are assumed to eliminate negativity of the influence stating that ducts are being produced properly [40],[41],[42],[43],[44],[45].

Together, hematological and histopathological markers provide a comprehensive assessment of systemic and local effects in experimental models. Their integration allows researchers to distinguish between agents that merely alleviate symptoms and those that genuinely restore physiological and structural integrity [46],[47]. In the present study, these markers were employed to evaluate the protective efficacy of *Asparagus racemosus* against NMU+Cisplatin-induced damage.

Traditional and Pharmacological Relevance of Asparagus racemosus:

Asparagus racemosus Willd., known as Shatavari, has been prized in Ayurvedic medicine for its euphoric and adaptogenic effects. The plant has been utilized over the ages to treat those conditions affecting women's reproductive organs and digestive system, as well as for promoting health in general. The meaning of the term Shatavari in Sanskrit is "one with a hundred husbands" suggesting its connection to the female gender [48],[49],[50],[51].

New research on Shatavari confirms that this plant contains a variety of active compounds such as steroidal saponins (shatvarins I-VI), flavonoids, alkaloids, and polyphenolic compounds that can influence the functioning of an organism. According to the results of contemporary studies on Shatavari, these compounds are able to exhibit their antioxidants, anti-inflammatory, immunomodulatory, and anti-cancer effects [52],[53],[54],[55],[56],[57],[58],[59].

A. racemosus's ability to function as an adaptogen is of relevance and, in particular, very interesting when it can mitigate the side effects of chemotherapy. The plant must reinforce the body so that it can effectively protect the bone marrow and other organs from the action of the chemotherapeutic drug cisplatin. Some of its properties, particularly antioxidant, can reduce oxidative stress, while immunomodulation can be useful in restoring the leukocyte count and improving immunity. It is also somewhat anticancerous, giving reason to postulate that this plant will prevent the process of carcinogenicity provoked by NMU, thus fencing off

the toxic effects of the carcinogens and chemotherapy [60],[61],[62],[63],[64],[65],[66],[67].

Various studies have attempted to establish the usefulness of *A. racemosus* in the treatment of diseases and toxicity. The extracts of the plant have also been indicated for gastric ulcers, neurotoxicity, and liver toxicity. However, in oncology, little work has been done on the ability of this plant to suppress tumors and increase the efficacy of standardized chemotherapy agents. However, there is still insufficient research in the area.

Study Rationale and Objectives:

Triple-negative breast cancer (TNBC) continues to be one of the most aggressive and difficult to treat types of breast cancer due to its molecular complexity and poor prognosis as well as its resistance to traditional treatment methods. With the lack of receptors for estrogen, progesterone, and HER2, this type of breast cancer cannot be treated with hormonal therapies. Chemotherapy remains the only option available. Nevertheless, chemotherapeutic drugs like cisplatin have very high systemic toxicity, resulting in the development of anemia, leukopenia, and tissue damage which negatively impact the quality of life of the patients. Therefore, there is a relevant need for supportive agents that can increase treatment efficacy with a diminished risk of side effects. Natural products, in particular the plant Asparagus racemosus (Shatavari), have attracted attention due to their ability to exert effects on various targets as well as their excellent safety profile. Used as a medicinal herb in the Ayurveda system, A. racemosus has been shown to possess a range of beneficial properties including antioxidant, anti-inflammatory, immune-modulating, and antitumor activities.

The NMU-induced mammary carcinogenesis model in animals offers a reliable method to study triple-negative breast cancer (TNBC) and its treatment. NMU causes the same mutations that can be seen in human TNBC cells, while cisplatin mimics the clinical chemotherapeutic conditions, however, this comes with substantial systemic toxicity. The current study aimed to evaluate the protective properties of A. racemosus extract in NMU-induced TNBC rats exposed to cisplatin. The key hypothesis is that A. racemosus reduces carcinogenesis and systemic toxic impact through oxidative stress modulation, inhibition of inflammatory signaling through and enhancing of apoptosis. The goals of the study were to determine blood collection to check for bone marrow recovery, assess mammary tissues pathology to evaluate its restoration, compare dose-dependent effects (500 mg/kg and 1000 mg/kg) and combine the results for more detailed explanations. Thus, the objectives of the current study help to establish A. racemosus as a potentially viable adjunct treatment for TNBC, based on the old ethnopharmacological experience and contemporary oncology.

MATERIALS AND METHODS:

Experimental Animals:

Healthy female Wistar rats with body weights in the range of 150–180 g were obtained from institutional animal facility. The animals were kept in standard laboratory conditions, where the temperature was controlled at about 22 ± 2 °C and relative humidity was kept at around 55 ± 5%, and the light/dark cycle was kept 12 h/12 h. The animals were given standard pellet diet and water freely. All the experiments adhered to the principles laid down in the committee for the purpose of control and supervision of experiments on animals (CPCSEA). The study was ethically approved by institutional animal ethics committee before the start of the experiment. Lastly, standard protocol of a week of acclimatization was performed.

Chemicals and Reagents:

N-methyl-N-nitrosourea (NMU) is a strong carcinogen responsible for the development of breast cancer. It was ordered from a registered supplier and prepared prior to its use with the help of acidic buffer. Platinum compound – cisplatin was ordered from a company and disinfected before its peritoneal injection. The roots of *Asparagus racemosus* were acquired from reliable suppliers, shade dried, and finally, crushed. Ethical extraction was employed in this investigation using Soxhlet apparatus, and the extract was made in a vacuum. The extract was kept at 4 degrees centigrade prior to its oral administration.

Experimental Design and Grouping:

The design of the experiment aimed to test the protective efficiency of *Asparagus racemosus* from NMU-induced mammary cancer and cisplatin-induced systemic toxicity in the Wistar rat model. After acclimatization, rats were randomly divided into four groups of 10 rats in order to avoid bias and ensure the experiment is repeatable.

Carcinogenesis was induced using a single intraperitoneal dose of N-methyl-N-nitrosourea (NMU) in a dose of 50 mg/kg body weight, freshly diluted in acidic buffer to keep it stable. The rats were observed for two weeks, in particular after the induction while waiting for any cancerous transformation to take place. This period between the injection and observation was used according to the recommendations of the previous studies proving that NMU has to take its time to perform the following processes: DNA alkylation plus mutagenesis taking place in the body, after which the evaluation of the treatment effects becomes proper.

Cisplatin was given on day 15 after NMU induction, using intraperitoneal administration of 3 mg/kg weekly for 6 weeks. The treatment was based upon the need to replicate chemotherapy cycles and to keep the acute toxic effect at a minimum. At the same time, A. racemosus extract was administered as a concomitant treatment (starting from day 15) in order to achieve the purpose of its use as an adjunct

agent. The extract was given orally every day over the entire period of study to evaluate both preventive and restorative effects.

Haematological Analysis:

Blood samples were obtained from the retro-orbital plexus while the process was being conducted under a light available anesthesia at specific times during the course of the study. The blood samples were transferred to EDTA-coated tubes so that blood clotting would not occur in them, and they were used for hematological evaluation immediately. The experiment aimed to evaluate RBC count, hemoglobin level, hematocrit, WBC count, and platelet count by using an automated analyzer specifically manufactured for evaluation of rodent blood parameters. All the above parameters were selected due to their sensitivity to the processes in the bone marrow, and due to the possibility of revealing the presence of toxic processes in the organism, especially concerning carcinogenic effects of NMU and treatment with cisplatin. Restoration of certain hematological parameters became a marker of whether the organism was restored and whether the action of Asparagus racemosus was effective.

Histopathological Examination:

Mammary tissues were harvested, preserved in a 10% neutral buffered formalin solution, and histologically examined at the conclusion of the experiments. Section examinations involved creating sections of paraffin wax area paraffin and cutting it into thin slices measuring 5 µm while staining these slices according to the standards with H&E. A microscope was applied for the investigation of how the mammary structures are arranged, how the ducts are formed and organized and where mucin is formed, etc. The expectations concerning the control group were that mammary tissues will reflect normal histological structure. The NMU with cisplatin experiment was forecasted to show the loss of organization in ducts and mucin accumulation. The evaluation of treatment with A. racemosus was made qualitatively and semi-quantitatively concerning restoration of ducts.

Statistical Analysis:

Results for the experiments were expressed as mean ± standard deviations (SD), with the number of subjects being (n = 10). The one-way ANOVA was used to determine the existence of differences in means within groups. Tukey's post hoc test was performed after the initial comparison had been made. In the current study, p-value less than 0.05 was taken to indicate statistical significance of the data. The given way of data statistical analysis was needed to completely evaluate the role of the Asparagus racemosus extract and support its conclusions statistically. It is worth mentioning that results were analyzed with the help of special software, and therefore collected data were presented in both graphical and tabular forms.

RESULTS:

Haematological Parameters:

Blood parameters showed statistically significant differences after the use of NMU and cisplatin, but they were reduced significantly due to the effect of *Asparagus racemosus*. The values of RBC ($5.8 \pm 0.4 \times 10^{12}$/L), hemoglobin ($14.1 \pm 0.7$ g/dL), hematocrit ($43.6 \pm 2.0\%$), WBC ($7.3 \pm 0.6 \times 10^{9}$/L), and platelets ($387 \pm 34 \times 10^{9}$/L) were within the norm in the control group (CG). On the contrary, a notable alteration took place in the NMU + cisplatin group represented by a drop in the number of RBC down to ($2.7 \pm 0.4 \times 10^{12}$/L), hemoglobin value to (5.8 ± 0.4 g/dL) and hematocrit to ($16.8 \pm 1.4\%$). In addition, the quantity of WBC reduced to ($3.9 \pm 0.5 \times 10^{9}$/L) and the number of platelets dropped to ($241 \pm 21 \times 10^{9}$/L). All of these values were statistically significant ($p < 0.05$) in comparison to the control group confirming the presence of anemia, leukopenia, and thrombocytopenia in the NMU + cisplatin group indicating bone marrow suppression and systemic toxicity of NMU and cisplatin respectively.

The treatment with extract from A. racemosus significantly improved the hematological values. The values at 500 mg/kg showed that red blood cell (RBC) count increased to $4.3 \pm 0.5 \times 10^{12}$/L, hemoglobin increased to 10.2 ± 0.6 g/dL, packed cell volume (PCV) was found to be $31.7 \pm 1.8\%$, white blood cell (WBC) count was equal to $5.8 \pm 0.4 \times 10^{9}$/L, and the platelet count was equal to $312 \pm 26 \times 10^{9}$/L. These values indicated only partial recovery of hematopoietic function with significant differences from the toxic group. The treatment with 1000 mg/kg of A. racemosus extract demonstrated nearly normal values such as $5.0 \pm 0.5 \times 10^{12}$/L of RBC count, 12.6 ± 0.7 g/dL of hemoglobin, $37.8 \pm 1.9\%$ of PCV, $6.5 \pm 0.5 \times 10^{9}$/L of WBC count, and $356 \pm 28 \times 10^{9}$/L of platelets. The obtained values were very close to those in the control group that confirmed the high effectiveness of protection and restoration. The obtained results indicate that extract from A. racemosus had a significant effect on recovery from hematological toxicity caused by NMU + cisplatin. The dose-dependent recovery shows the potential of this extract in supporting bone marrow functions in alleviating anemia and leukopenia and restoring homeostasis in the human body during the process of carcinogenesis and chemotherapy.

Table 1. Effect of Asparagus racemosus extract on hematological parameters in NMU + cisplatin-induced TNBC rats.

Group	RBC ($\times 10^{12}$/L)	Hb (g/dL)	PCV (%)	WBC ($\times 10^{9}$/L)	Platelets ($\times 10^{9}$/L)

Control (untreated)	5.8 ± 0.4[a]	14.1 ± 0.7[a]	43.6 ± 2.0[a]	7.3 ± 0.6[a]	387 ± 34[a]
NMU + Cisplatin	2.7 ± 0.4[c]	5.8 ± 0.4[c]	16.8 ± 1.4[c]	3.9 ± 0.5[c]	241 ± 21[c]
NMU + Asparagus racemose 500 mg/kg	4.3 ± 0.5[b]	10.2 ± 0.6[b]	31.7 ± 1.8[b]	5.8 ± 0.4[b]	312 ± 26[b]
NMU + Asparagus racemose 1000 mg/kg	5.0 ± 0.5[b]	12.6 ± 0.7[b]	37.8 ± 1.9[b]	6.5 ± 0.5[b]	356 ± 28[b]

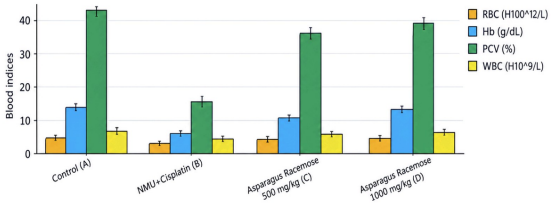


Figure 1. Effect of Asparagus racemosus extract on hematological parameters in NMU + cisplatin-induced TNBC rats. (A) Control group; (B) NMU + cisplatin group; (C) NMU + Asparagus racemosus 500 mg/kg group; and (D) NMU + Asparagus racemosus 1000 mg/kg group.

Values are expressed as mean ± SD (n = 10). RBC, red blood cell count; Hb, hemoglobin; PCV, packed cell volume; WBC, white blood cell count.

Histopathological Findings

A histopathological assessment of mammary gland samples indicated drastic evidence of the damaging effects of NMU and cisplatin, as well as the healing power of the *Asparagus racemosus* extract. Results obtained for the control group on the histopathology of their mammary gland tissues (Figure 8A) indicated the normal histoarchitecture of the tissues characterized by normal adipocytes pattern and unbroken ductal structures. It has been evident from the distribution of the ducts in connective tissue and cell structure patterns seen in the images that the physiologic functioning of the gland is normal and free of pathologic lesions.

On the contrary, the NMU + cisplatin group of tissues (Figure 8B) revealed a number of histologically noticeable changes. The histopathology of mammary gland tissues of this group revealed visible disorganization with disrupted ductal structures, mucin deposits in the ductal lumen, and the signs of variable fibrous connective tissues proliferation. By observing the epithelial linings of the ducts in the images, we noticed an irregular and hyperplastic appearance, which indicates that the process of carcinogenesis was going on as a response to the chemical damage caused by NMU.

Treatment with A. racemosus has enhanced tissue morphology significantly. In 500 mg/kg (Figure 8C) dose treatment, the ductal arrangement has been partially restored as some of the ductal structures and adipocytes are visible in the parenchyma of the treated animals. The matrix has been established, but mild fibrosis is still observed in comparison to the NMU + Cisplatin group indicating the initial stages of recovery at the level of the glands. In 100 mg/kg dose group (Figure 8D), the almost normal histological features were observed, with clearly visible ducts and the presence of adipocytes similar to the control group. Moreover, there was less fibrosis in the interstitium, as well as minimal changes in mucin deposition, proving the fact that substantial reversal of the damage caused by carcinogens and chemotoxic agents has taken place. In summary, all of these findings indicate that the A. racemosus has a protective dose-dependent effect on the mammary tissue's architecture and that the highest dose (1000 mg/kg) achieved almost normal histological features.

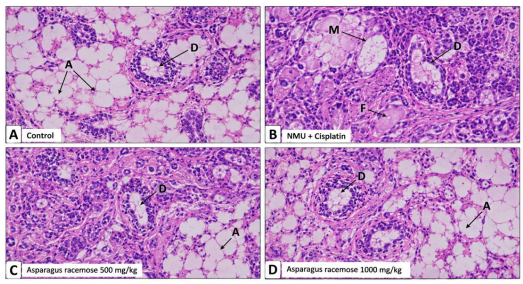


Figure 2. Histopathological examination of rat mammary tissue (H&E staining, ×500). (A) Control group showing normal mammary tissue architecture with well-organized adipocytes and intact ductal structures. (B) NMU + cisplatin group showing marked tissue disorganization, mucin deposition within ducts, disrupted ductal structures, and increased fibrous connective tissue. (C) A. racemosus 500 mg/kg group showing partial restoration of mammary tissue architecture with visible ducts and adipocytes. (D) A. racemosus 1000 mg/kg group showing near-normal histological features with well-defined ducts and adipocytes.

DISCUSSION

The present study shows the association of NMU and cisplatin in significant local and systemic adverse effects including increased severity of anemia, leukopenia, thrombocytopenia, and disruption of the structure of mammary tissue. This is attributed to the mechanism of action of NMU as a DNA-alkylating carcinogen and the action of cisplatin as a chemotherapeutic agent that works through causing DNA adducts and free radicals that create oxidative stress and apoptosis as well as hematopoietic dysfunctions. Decrease in blood parameters in the group exposed to toxicity correlates with the statement about the disturbed processes in hematopoiesis while results of histological analysis indicate the disorganization of the ductal tissue.

The use of Asparagus racemosus extract significantly reduces the negative consequences of toxic action which supports the notion of the agent functioning as a restorative/protecting agent. The increase in the number of the blood components confirms the information regarding the recovery of the normal functions of the bone marrow and the body. Restoration of the structure of the ducts and organization of the adipocytes is also proof of the effectiveness in protecting the structure of the mammary gland. The action of the phytoconstituents of Asparagus racemosus, such as flavonoids, steroidal saponins, and polyphenols, that exert their antioxidant, anti-inflammatory, and immunomodulatory effect is responsible for its protective action.

The results of the experiment also indicate a strong dose-dependent effect. With a dose of 500 mg/kg of A. racemosus, there was some improvement in hematological parameters and moderate improvement in the tissue structure. However, when A. racemosus was used at a dose of 1000 mg/kg, the results were close to those of the control group. This indicates the importance of the use of higher doses of A. racemosus for the effective prevention of chemotoxicity and carcinogenesis. Furthermore, the strong relationship between hematological and histopathological recovery of tissues indicates that the cure of blood conditions leads to the cure of tissues.

These results align with earlier findings regarding the adaptogenic as well as the cytoprotective properties associated with A. racemosus, as well as other similar medicinal plants like Withania somnifera and Tinospora cordifolia that have shown similar impacts in studies on oxidative stress and chemotherapy-associated toxicity. Nonetheless, the present study furthers this evidence on TNBC as it establishes that A. racemosus reduces not only systemic toxicity but also helps in restoring mammary tissue integrity depending on the dosage used. The data presented in this research study thus allow for making A. racemosus a promising adjunct in the cancer therapy, as it has the capability of making the treatment more tolerable, reducing the side effect substansially and even ultimately improving the therapeutic outcome.

CONCLUSION

This research proves that *Asparagus racemosus* is highly effective against NMU and cisplatin toxicity. The extract has positive effects on red blood cells (RBC), hemoglobin (Hb), packed cell volume (PCV), white blood cells (WBC), and platelet counts. In histopathological studies, tissue organization was preserved and fibrosis was found to be decreased after treatment with A. racemosus, thus confirming the results. The findings highlight the numerous benefits of the plant. It is known to have anti-oxidant, anti-inflammatory and immunomodulatory properties that help to support the processes in the bone marrow and protect the breast tissues. Based on the correlation between blood parameters restoration and recovery of tissues, one can judge about the generalized and local protective effects of A. racemosus. In general, this means that A. racemosus can be applied in treatment protocols of tumors as a tool to mitigate the side effects of chemotherapy and to provide for recovery processes. Nonetheless, additional research needs to be carried out in order to determine its mode of action and areas of application in the clinical setting.

ABBREVIATIONS

TNBC: Triple-Negative Breast Cancer
ER: Estrogen Receptor
PR: Progesterone Receptor
HER2: Human Epidermal Growth Factor Receptor 2
NMU: N-methyl-N-nitrosourea
RBC: Red Blood Cells
Hb: Hemoglobin
PCV: Packed Cell Volume
WBC: White Blood Cells

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