# Effectiveness of Nanotechnology for Drugs in Patients with Cancer: Integrative Literature Review

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*Efetividade da Nanotecnologia para Medicamentos em Pacientes com Câncer: Revisão Integrativa da Literatura*

Efectividad de la Nanotecnología para Fármacos en Pacientes con Cáncer: Revisión Integrativa de la Literatura

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***ABSTRACT***

**Introduction:** Nanotechnology consists of the control and manipulation of matter at atomic and molecular level, allowing the development of devices, materials, and systems with properties different from those observed in the micro or macroscopic scale. **Objective:** Verify scientific evidence about the effectiveness of drugs in patients with cancer utilizing nanotechnology. **Method:** Integrative review of the literature. The search for articles was carried out in the databases MEDLINE (PubMed), LILACS, SciELO, Scopus, Web of Science e BVS. There was no restriction of location, period, and language. For the selection of the studies, the combination based on the Medical Subject Heading Terms (MeSH) was used. Studies that scored ≥ 6 points according to the qualitative scoring protocol were included in the study. **Results:** 216 articles were found, and after the elimination of duplicates, 208 remained. The titles and abstracts were analyzed, and 205 papers were excluded because they were not within the scope of the proposed study. Three articles of the type clinical trial were admitted for the final analysis. The nano complexes showed efficiency in the samples presented, being effective when the objective was to delay the progression of certain types of cancers. **Conclusion:** Medications with nanoparticles used in the studies showed good adherence by the patients, in addition to effectiveness in the treatment of specific cancers. However, additional studies are needed to explore the activity of these drugs.

**Key words**: Nanotechnology; Nanoparticles/therapeutic use; Access to Essential Medicines and Health Technologies; Drug Utilization; Neoplasms.

RESUMO

**Introdução:** A nanotecnologia consiste no controle e manipulação da matéria em nível atômico e molecular, permitindo o desenvolvimento de dispositivos, materiais e sistemas com propriedades diferentes daquelas observadas na escala micro ou macroscópica. **Objetivo:** Verificar evidências científicas sobre a efetividade dos medicamentos em pacientes com câncer pelo uso da nanotecnologia. **Método:** Trata-se de uma revisão integrativa da literatura. A busca de artigos foi realizada nas bases de dados MEDLINE (PubMed), LILACS, SciELO, *Scopus*, *Web of Science* e BVS. Não houve restrição de localização, período e idioma. Para a seleção dos estudos, foi utilizada a combinação baseada no *Medical Subject Heading Terms* (MeSH). Incluíram-se na pesquisa estudos que obtiveram pontuação ≥ a 6 pontos, segundo o protocolo para pontuação qualitativa. **Resultados:** Foram localizados 216 artigos, sendo totalizados 208 após verificação por duplicação. Em seguida, os títulos e resumos foram analisados, sendo excluídos 205 trabalhos fora do escopo da proposta da pesquisa. Admitiram--se, para a análise final, três artigos do tipo estudo clínico. Os nanocomplexos apresentaram eficiência nas amostras apresentadas, sendo eficazes quando o objetivo consistia em retardar a progressão de determinados tipos de cânceres. **Conclusão:** Os medicamentos com nanopartículas utilizados nos estudos demonstraram boa adesão pelos pacientes, assim como se apresentaram eficazes no tratamento de cânceres específicos. Contudo, estudos adicionais são necessários para explorar a atividade desses medicamentos.

**Palavras-chave:** Nanotecnologia; Nanopartículas/uso terapêutico; Acesso a Medicamentos Essenciais e Tecnologias em Saúde; Uso de Medicamentos; Neoplasias.

RESUMEN

**Introducción:** La nanotecnología consiste en el control y manipulación de la materia a nivel atómico y molecular, permitiendo el desarrollo de dispositivos, materiales y sistemas con propiedades diferentes a las observadas a escala micro o macroscópica. **Objetivo:** Verificar la evidencia científica sobre la efectividad de los medicamentos en pacientes con cáncer mediante el uso de nanotecnología. **Método:** Se trata de una revisión integrativa de la literatura. La búsqueda de artículos se realizó en las bases de datos MEDLINE (PubMed), LILACS, SciELO, Scopus, *Web of Science* e BVS. No hubo restricción de ubicación, período e idioma. Para la selección de estúdios, se utilizó la combinación basada en los Términos de Encabezamiento de Materia Médica (MeSH). Los estudios que puntuaron ≥ 6 puntos según el protocolo de puntuación cualitativa. **Resultados:** Se encontraron 216 artículos, con un total de 208 luego de la verificación por duplicación. Luego, se analizaron los títulos y resúmenes, y se excluyeron 205 artículos por no estar en el alcance de la propuesta de investigación. Se admitieron tres artículos del tipo estudio clínico para el análisis final. Los nano complejos mostraron eficiencia en las muestras presentadas, siendo efectivas cuando el objetivo era retrasar la progresión de ciertos tipos de cánceres. **Conclusión:** Los fármacos de nanopartículas utilizados en los estudios mostraron una buena adherencia por parte de los pacientes, además de ser eficaces en el tratamiento de cánceres específicos. Sin embargo, se necesitan estudios adicionales para explorar la actividad de estos fármacos.

**Palabras clave:** Nanotecnología; Nanopartículas/uso terapéutico; Acceso a Medicamentos Esenciales y Tecnologías Sanitarias; Utilización de Medicamentos; Neoplasias.

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## INTRODUCTION

Cancer consists of more than 100 diseases having in common the abnormal growth of cells invading tissues and organs. The cells tend to be aggressive contributing for the formation of tumors and can spread to other parts of the body. The different types of cancer correspond to different cells associated, the characteristics of their differentiation is the speed of multiplication of the cells and the capacity of affecting other tissues and organs[1].

It is the second main cause of death in the world, causing the decease of nearly 9.6 million individuals in 2018. From 2020 until 2022, 625,000 cases are estimated for each year[2]. Although the incidence is still higher in developed countries, mortality has been lowering in underdeveloped countries, a difference reflecting the different profiles of the disease and access to diagnosis and treatment[3].

The treatment of cancer is challenging. In despite of recent progress and new studies, the treatments available consist of surgery, radiotherapy, chemotherapy, and immunotherapy with regular adverse events as drug resistance and pharmacologic issues in addition to toxicity associated with side effects mostly impacting the patient's quality of life[4]. The investment in nanotechnology has been growing and consists in the control and manipulation of matter at atomic and molecular level allowing the development of devices, materials, and systems with remarkable different properties in comparison with those at micro or macroscopic scale[5].

It is anticipated that certain shortcomings currently identified in cancer treatment are eventually resolved and/or minimized with the advances of nanotechnology considering the characteristics of the nanomaterials as the relation surface/volume, form, size, introduction of targeting molecules and physical-chemical improvements of the components[6].

The current study has the main objective of analyzing scientific evidence about the efficacy of the drugs in patients with cancer using nanotechnology to respond to the following research question: What is the efficacy of the administration of drugs by nanotechnology in patients with cancer?

## METHOD

Integrative review of the literature. Two independent investigators searched for scientific articles in the electronic databases (PubMed), LILACS, SciELO, Scopus, Web of Science and BVS, no language, period, and location restrictions. The integrative review consists in a method that favors the incorporation of the applicability of significant studies in the practice with emphasis in reviews, allowing the inclusion of experimental and non-experimental studies for better understanding of the phenomenon analyzed[7].

The descriptors were selected from the controlled concepts of Descriptors of Sciences of Health (DeCS) and Medical Subject Heading Terms (MeSH), based in the great utilization by the scientific community for indexing articles in the database PubMed. After the search of the descriptors conducted in September 2020, the adequacy to the other bases used was made. The following descriptors were proposed for the search: cancer AND nanotechnology AND treatment AND (pharmaceutical preparations OR receptors drug) and the Boolean operators: and/or. As the objective was to analyze the efficacy, the descriptor of the reference cancer AND nanotechnology AND treatment AND effectiveness, and the Boolean operator were utilized.

No restrictions were defined for the studies' design regarding the type evaluated. Studies with score ≥6 points according to the protocol of qualitative scoring proposed by Pithon et al[8] and without language, period and location requirements were included.

The reviewers evaluated independently the quality of the methods utilized in the studies included. The evaluation prioritized the clear description of the information where the names of the authors were blinded and reviewed to avoid any bias and conflict of interests.

The extraction of the data for eligibility was carried out with a proprietary form for systematic review that two investigators created in Excel®, where the data extracted were added by one of the investigator and checked by the other investigator. Initially, they were selected by the title; next, the abstracts were reviewed and only the potentially eligible were chosen. Based in the abstracts, the articles were selected for full reading and those that met all the pre-determined criteria were selected.

Firstly, the eligibility screening was calibrated for systematic review. The articles whose titles were within the scope, but the abstracts weren't available were collected and reviewed fully as well. Studies out of the scope, case reports, letters to editor and/or editorial, indexes, abstracts, and studies with animal models were excluded. Later, the full text of the eligible studies were initially evaluated. In specific cases, when the potential eligibility was detected but the data were incomplete, the authors could be contacted by e-mail for more information, however, in the current study it was not necessary.

After screening, the text of the article selected was reviewed and extracted according to a standard by two authors identifying the year of publication, country, language, type, sample, method, result, and conclusion.

The clinical outcome of interest consisted in analyzing the efficacy of the drugs in patients with cancer using nanotechnology. Those who did not use the approach proposed were not included in the sample of the integrative review. Considering that the texts had to contain simultaneously the expressions "pharmaceutical preparations" and "Receptors Drug" in the traditional fields of search (title, abstract and keywords), the search may have been restricted. Possibly, some articles that the authors utilized only one of these expressions in these fields may have been excluded.

## RESULTS

Initially, 216 articles were selected, remaining only 208 after duplication checking. Next, titles and abstracts were reviewed, and 205 articles were excluded because they were out of the scope. The three studies accepted scored 12 points in the modified protocol of Pithon et al.[8] for evaluation of quality. Eventually, three clinical type articles were chosen for final analysis[9-11] (Figure 1).

In the first study selected[9], the authors indicate that the Engeneic Delivery Vehicle (EDV) is recognized as a novel nanocellular compound (mini-cell), which packages theoretically effective concentrations of chemotherapeutic drugs designed to target tumors via mini-cell-surface attached bispecific proteins. With this, the main objective of the study was to determine the maximum tolerated dose (MTD) of EDV in patients with recurrent glioblastoma (GBM).

The sample consisted of 14 patients in three groups of doses treated in 8-week cycles. It was utilized a standard 3+3 dose scaling to evaluate three groups of dose. Level 1 (2x10^9 EDV) was formed by three patients similar to level 2 (5x10^9 EDV) and eight in level 3 (8x10^9 EDV). Six patients failed to complete one treatment cycle because of the progression of the disease. In all, three patients completed four cycles of treatment[8]. All the tumors expressed epidermal growth factor receptor (EGFR). No patient had dose-limiting toxicity (DLT), and none was removed from the study because of adverse event; treatment-related deaths did not occur[8].

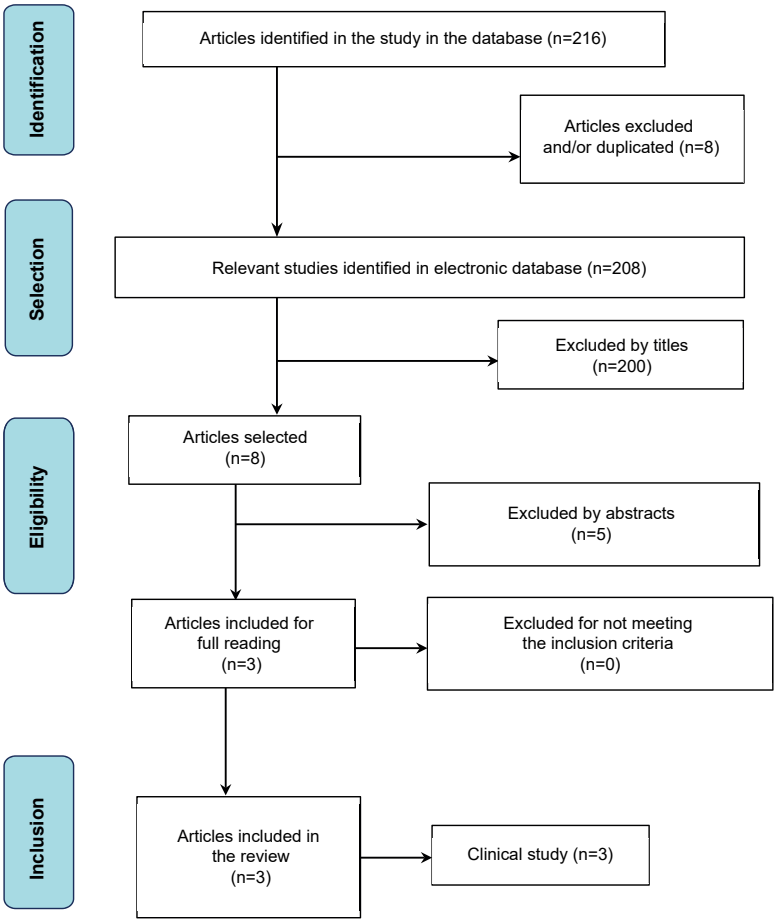


**Figure 1**. Flowchart of search and analysis of articles

A total of 8-week 21 complete cycles of EDV were administered in eight patients and was well tolerated by most of them. The typical symptoms more common were nausea (n=7 patients), fever (n=5 patients) and chills (n=5 patients). The majority presented slight increase of leukocytes and neutrophils from three to 24 hours after the dose intake. Except one patient with high levels of cytokines in the beginning of the study, all the others had transient increase of interleukins IL-6, IL-8 and IL-10, 3 hours after the first dose and returned to baseline 24 hours after measurement[9]. The response of the 14 patients was evaluated, of which, eight completed one cycle (eight doses). The best response was stable disease in four patients (28%), one patient in level 1, two in level 2 and one in level 3 had stable disease after cycle 3[9]. The study showed that EDV can be administered safely in patients with recurrent GBM with maximum dose of treatment of 5x10^9 EDV[9].

In the second[10], 13 patients previously treated for metastatic genitourinary cancer were included in the sample. The authors developed a systemically administered tumor-targeted liposomal nanodelivery complex (SGT-94), carrying a plasmid encoding RB94, a truncated form of the RB gene. In pre-clinical studies, RB94 showed efficacy against the tumor. Of these, 11 patients had urothelial cancer, one, prostate cancer and one, urachus cancer. All the patients received at least one dose of SGT-94, being this a new agent of systemic genic therapy targeted to tumors. Nearly 11 patients were considered evaluable to receive this compound and measure the DLT.

Most of the adverse events observed in the evaluable patients were grades 1 and 2, the most frequent toxicity recorded being grade 1/2 thrombocytopenia (45% of the subjects). The hematological effects were typically transient and improved as the patients continued therapy. Fever and chills were experienced by 27% of the patients. In addition, two subjects (18%) had lymphopenia grades 1 or 2 or decrease in leukocytes count. Of the grades 3 and 4 adverse events that the study found, only three were deemed possibly related to SGT-94. All of these adverse events, including grades 3 and 4 were transient and resolved while continuing treatment[10]. In conclusion, systemically delivered SGT-94 showed evidence of selective tumor-targeting and was well tolerated by the patients[10].

The third[11] had the objective of investigating the intervention of nanotechnology through reproducible formulations and clinical evaluations. The study evaluated six patients with stage III A or III B breast cancer. The individuals were divided in two groups. The patients of group A received injection of doxorubicin, 60 mg every three weeks with 1-hour intravenous infusion. In addition, this group of patients has also received injection of cyclophosphamide, 600 mg every three weeks with 1-hour intravenous infusion. Firstly, it was applied in mice with breast cancer and late in humans. The patients of group B received injection of doxorubicin, 60 mg every three weeks with 1-hour intravenous infusion. In addition, this group received two tablets, three times a day after the meals of the experimental study drug Nano Swarna Bhasma (NSB). The base surface area (BSA) was utilized to calculate the doses for each patient. Four of these cycles were repeated for 12-weeks. The authors made proprietary combinations of gold nanoparticles and phytochemicals of mango, curcumin, gooseberries, and gum Arabic to develop NSB through nanotechnology[11].

The lesion that cancer provoked in group B (standard treatment together with the medication NSB) was reduced in the 7th. week and more reduced in week 12 in comparison with the initial measurements. Considering that in group A – who received the standard treatment – the lesion increased in week 7. The progressive response of the disease was found in one patient (33.3%) during the whole period of the treatment in group A while none of the patients had disease progression in group B. At the end of the treatments, in week 12, clinical benefit rate/ disease control rate was calculated for all the patients[11].

The patients treated with NSB drug along with the standard of care treatment (group B) exhibited 100% clinical benefit rate when compared with group A who received standard of care treatment. Based on this, the authors indicated there was acceptable safety and efficacy results in patients with breast cancer. Administering of the NSB drug in patients with breast cancer did not show adverse effects as monitored through both vital signs and laboratory chemistries. Commonly reported adverse events were transient implying acceptable safety. The results also indicate that NSB can be safely used as a valuable adjuvant therapeutic agent to reduce the adverse effects of routine chemotherapeutic agents while providing measurable therapeutic efficacy in treating breast cancer. Nanotechnology-based formulations such as NSB drug show minimal toxicity to normal cells and tissues[11].

The main detailed characteristics of the studies are shown in Table 1.

## DISCUSSION

The current study tried to check scientific evidences about the efficacy of the administration of drugs by nanotechnology in patients with cancer. In the studies analyzed[9-11], it was concluded that the drugs with nanoparticles utilized in the study demonstrated good adherence by the patients being also effective in the

Table 1. Summary of the articles included

| Author/year Country of publication | Objective | N of the sample | Type of cancer | Method | Results | Conclusion |
|---|---|---|---|---|---|---|
| Whittle et al., 2015 Australia | Determine the maximum dose tolerated of EDV in patients with recurrent glioblastoma | 14, mean age of 55 (35-71) years of age, 7 men and 7 women | Recurrent Glioblastoma | Patients in three strata of dose treated with 8-week cycles. Level 1 (2x10 of EDV) consisted of three patients as similar to level 2 (5x10EDV) and eight in level 3 (8x10 EDV) | The most common symptoms were nausea, fever or chills experienced by 7, 5 and 5 patients respectively. Most of the patients had a mild self-limited increase of leukocytes and neutrophils in 3-24 hours after the dose | EDV can be administered safely in patients with recurrent glioblastoma with maximum dose of treatment of 5x10 EDV. However, this study was the first to evaluate this new technology. Other pre-clinical studies and of biodistribution should be considered |
| Siefker-Radtke et al., 2016 USA | Verify the effectiveness of SGT-94 in patients with genitourinary cancers | 13, mean age of 67, being 3 women and 10 men | Genitourinary cancers | Patients received at least one dose of SGT-94 | Most of the adverse events found in evaluable patients were from grades 1 and 2 with toxicity. Fever and chills were experienced by 27% of the patients. In addition, 2 individuals (18%) had lymphopenia grades 1 and 2 or decreased leukocytes count | SGT-94 administered systemically showed evidence of selective targeting of tumor and was well tolerated by the patients. Additional studies are necessary to explore the activity of this drug as single agent and in combined therapy |
| Khoobchandani et al., 2020 USA | Investigate the intervention of nanotechnology through reproducible formulations and clinical evaluations | 6, age between 18 and 65 years of age | Breast cancer | Patients divided in two groups (A and B), injection of doxorubicin, concentration of 60 mg every 3 weeks as intravenous infusion of 1 hour, injection of cyclophosphamide, concentration of 600 mg every three weeks with intravenous infusion of 1 hour. Group A received only traditional treatment and group B received traditional treatment and intake of NSB | The administration of the drug NSB in patients with breast cancer did not cause adverse events, monitored through vital signs and lab chemistries. Commonly related adverse events were transient, implying in acceptable safety | The results indicate also that NSB can be used safely as an adjuvant therapeutic agent to reduce the adverse events of the routine chemotherapeutic agents while providing measurable therapeutic to treat breast cancer |

**Captions:** NSB = Nano Swarna Bhasma; SGT-94 = Liposomal nanocomplex; EDV = Engeneic Delivery Vehicle.

treatment of specific cancers investigated in each study.

In the first[9], the authors utilized EDV in patients with GBM, the doses for the participants were categorized in three levels; level 1 (2x10^9 of EDV) applied in three patients as well as in level 2 (5x10^9 EDV) and eight in level 3 (8x10^9 EDV). The authors quote that the best response found was stable disease in four patients (28%), one patient in level 1, two in level 2 and one in level 3 presented stable disease after cycle 3. With this, the study demonstrated that EDV can be administered safely in patients with recurring GBM with maximal dose of treatment of 5x10^9 EDV.

Nanotechnology has been contributing significantly to foster advances in the medical area. It is still difficult to predict whether the toxic effects of these nanosystems would be related only to the drug associated or if nanostructuring would bring some additional adverse effect to the drug. However, it is extremely relevant that for the sake of the patient's safety, nanostructured drugs are investigated in clinical trials evaluating its therapeutic efficacy[12] before its commercial sale.

Gold nanoparticles (AuNPs) are being studied frequently. In a review study, the authors described that the fast progress of nanotechnology in the last years has been encouraging the raising interest in the research of nanoparticles, specifically its application in cancer treatment and nowadays this is actually occurring. AuNPs can be used as delivery agents of drugs targeted to cancer

cells or in genetic therapy. According to the study, these particles have many invaluable properties to treat tumors, AuNPS are small and can penetrate widely and deposit in the tumor site and have good biocompatibility. The application of AuNPs in the treatment of tumor is quite considerable and promising[13].

One of the studies selected for this study[11] utilized gold nanoparticles as components present in the nanoparticles deposited in the drug. As result, the patients treated with the drug along with the gold standard of care treatment exhibited significant clinical benefit rate when compared to the other group receiving only the standard of care treatment. Administering the drug did not show significant adverse events as monitored. The results show that the drug can be used as adjuvant therapeutic agent to reduce the adverse effects of chemotherapeutic agents.

Furthermore, studies are demonstrating that the effectiveness of nanoparticles make them drug delivery carriers, utilized successfully in cancer treatment. Clearly, nanomaterials are effective in nanomedicine. However, the main obstacle is to predict the time to standardize and rule these assets[14.]

In another study included in this research[10], the authors developed an SGT-94 which was administered systemically. All the patients received at least one dose of SGT-94, being this a new agent of tumor-targeting systemic genic therapy. Of the 3 and 4 adverse events detected, only three were considered possibly related to SGT-94. All of them, including grades 3 and 4 were transient and resolved in the continuation of the treatment. In conclusion, administering SGT-94 systemically is effective and well tolerated by the patients[10].

Nanotechnology is gaining significant attention worldwide for cancer treatment. Nanobiotechnology encourages the combination of diagnostics with therapeutics. Nanoparticles are being used as nanomedicine which participates in diagnosis and treatment of various diseases, including cancer. The objective of the authors was to offer a perspective of several facets of nanotechnology in cancer therapeutic such as diverse nanomaterials as drug vehicles, a drug release strategy delivery and role of nanotechnology in cancer therapy[15].

The authors quote that cancer nanotechnology confers a unique technology against this disease through early diagnosis, prevention, and personalized therapy by utilizing nanoparticles. Nanobiotechnology plays an important role in the discovery of cancer biomarkers. Quantum dots, gold nanoparticles, magnetic nanoparticles, carbon nanotubes, gold nanowires etc. have been developed as a carrier of biomolecules that can detect cancer biomarkers. Nanoparticle assisted cancer detection and monitoring involves biomolecules like proteins, antibody fragments, DNA fragments, and RNA fragments as the base of cancer biomarkers[15]. The use of nanocarriers as method of drugs delivery can potentialize the pharmacologic properties of the compounds normally utilized in cancer treatment[16].

## CONCLUSION

Nanoparticles utilized in the studies for several types of cancer analyzed showed good patients' adherence and seem to be effective for the treatment of specific cancers, as the adverse events reported were transient with acceptable safety. However, additional researches are needed to explore the activity of these drugs as single agent and in combined therapy, in addition to broaden the number of patients investigated. Furthermore, certain nanoparticles have functionalities that potentialize the anticarcinogenic effects of the antineoplastic drugs and appear as a new approach for cancer treatments.

Certain nanoparticles, with diverse chemical properties and mechanisms of generation have toxic effects against different tumor cells and can have more effective antitumor impact in certain tumor lineages. Despite the good results involving nanoparticles and antineoplastics, adverse events caused by toxicity from production needs to be discussed and evaluated thoroughly.

### CONTRIBUTIONS

Both authors contributed substantially for the study design and conception, collection, analysis and/or interpretation of the data, wording, and critical review. The authors approved the final version to be published.

### DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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