



NATURAL RUBBER LATEX AND BIOMEMBRANES IN BIOMEDICAL APPLICATIONS: DO ITS EFFECTS JUSTIFY ITS USE?

LÁTEX DE BORRACHA NATURAL E BIOMEMBRANAS EM APLICAÇÕES BIOMÉDICAS: SEUS EFEITOS JUSTIFICAM SEU USO?

Luciana Mascena Silva^{1*}, Davide Carlos Joaquim², Arthur Castro de Lima³, Ana Karine Rocha de Melo Leite⁴, Ana Caroline Rocha de Melo Leite⁵, Virgínia Cláudia Carneiro Girão-Carmona⁶

¹Doctorate of the Postgraduate Program in Morphofunctional Sciences of the Federal University of Ceará (UFC), Fortaleza (CE), Brazil, ²PhD from the Postgraduate Program in Morphofunctional Sciences of the Federal University of Ceará (UFC), Fortaleza (CE), Brazil, ³Master of the Postgraduate Program in Morphofunctional Sciences of the Federal University of Ceará (UFC), Fortaleza (CE), Brazil, ⁴Doctor of Medical Sciences by the Federal University of Ceará (UFC) and assistant professor of the Graduate Course in Medicine of the State University of Ceará (UECE), Quixeramobim (CE), Brazil, ⁵Doctor of Medical Sciences from the Federal University of Ceará (UFC), adjunct professor of the Graduate Course in Nursing and Pharmacy of the University of the International Integration of Afro-Brazilian Portuguese (UNILAB) and permanent lecturer and supervisor of the Postgraduate Program in Nursing UNILAB, Redenção (CE), Brazil, ⁶Doctor of Pharmacology from the Federal University of Ceará (UFC), assistant professor of the Graduate Course in Medicine of the Federal University of Ceará (UNILAB) and permanent lecturer and supervisor of the Postgraduate Program in Morphofunctional Sciences of the Federal University of Ceará (UFC), Fortaleza (CE), Brazil.

***Corresponding author:** Luciana Mascena
Email: lumascena2@gmail.com

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ABSTRACT: This study aimed to gather the literature on the biomedical applications of natural rubber latex (NRL). This integrative review, carried out in 2021, based on the guiding question “What are the biomedical applications of NRL?” was developed using the PICO strategy. The combination of the words “Natural Rubber” AND “Biomaterials” was used in the databases’ search. The 23 articles addressed, as biomedical objectives/applications, the incorporation of drugs/products into the NRL membrane in phenomena such as microbial action, pain, and adverse events. Regarding the results of this incorporation, the publications indicated an occurrence dependent on the density and size of the pores, in addition to the absence of structural changes and significant interactions with the membrane. Furthermore, the release of the drugs/products was initially rapid. It is concluded that the works focused on research addressing the incorporation of drugs/release products into the NRL membrane, dependent on its inherent properties and with different effects, without harm to other cell types.

KEYWORDS: Biomaterial. *Hevea brasiliensis*. Latex. Rubber.

RESUMO: Este trabalho objetivou reunir a literatura sobre as aplicações biomédicas do látex de borracha natural (LBN). Trata-se de revisão integrativa, realizada em 2021, baseada na pergunta norteadora “Quais as aplicações biomédicas do LBN?”, elaborada a partir da estratégia PICO. A combinação de palavras “Natural Rubber” AND “Biomaterials” foi utilizada na busca nas bases de dados. Os 23 artigos inclusos abordaram, como objetivos/aplicações biomédicas, a incorporação de fármacos/produtos à membrana de LB nem fenômenos, como atuação microbiana, dor e eventos adversos. Quanto aos resultados dessa incorporação, as publicações indicaram ocorrência dependente da densidade e tamanho dos poros, além da ausência de alterações estruturais e interações significativas com a membrana. Ainda, a liberação dos fármacos/produtos era, inicialmente, rápida. Conclui-se que os trabalhos concentraram-se em pesquisas abordando incorporação de fármacos/produtos de liberação à membrana de LBN, dependente de propriedades inerentes a ela e com diversos efeitos, sem prejuízo para diferentes tipos celulares.

PALAVRAS-CHAVE: Biomateriais. Borracha. *Hevea brasiliensis*. Látex.

INTRODUCTION

Since ancient civilizations, the search for biomaterials capable of replacing natural organs and tissues has been a reality.¹ Faced with this challenge and with scientific progress, the elaboration of these substances has become one of the most relevant focuses of studies in Medicine and Bioengineering, especially due to their ability to restore human tissues affected by diseases or injured by accidents.² The achievement of this purpose is evident in studies that demonstrate the use of natural biomaterials such as collagen and chitosan in skin regeneration and antimicrobial applications, respectively.³

In addition to their applicability in health, such as tissue regeneration, implants, and drug delivery systems, biomaterials have been adopted in other areas. In environmental sectors, biomaterials are being explored for sustainable solutions, such as biodegradable packaging and water filtration systems. Moreover, in manufacturing, these materials are being integrated into producing bio-based composites and smart devices.

In Brazil, recent studies have focused on the development and application of biomaterials for bone regeneration, particularly in orthopedics and dentistry. Researchers have explored various degradable biomaterials and metallic biomaterials to create scaffolds that support bone tissue engineering. These scaffolds mimic native tissue and restore, maintain, or improve tissue function by combining cells, biomaterials, and bioactive factors. The economic impact of these biomaterials has also been evaluated, especially during the pandemic, highlighting the importance of market knowledge for clinical planning and decision-making.

In view of this perspective, many natural and synthetic polymers began to be used as a biomaterial, aiming to restore, maintain and improve tissue and its functionality. Among them, natural rubber latex (NRL), a biopolymer obtained from the rubber tree *Hevea brasiliensis*, stands out for its use in the biomedical area due to the low percentage of rejection by the human body and induction of allergic reactions, in addition to high mechanical resistance and ability to form a biofilm.² Added to this, this latex has the potential for exploitation, easy handling, and low cost, associated with the non-transmissibility of infectious agents.³

Obtained from bleeding *H. brasiliensis* tissues, particularly lactiferous ones, NRL is a colloidal, polyphasic and polydisperse system, consisting of a rubber phase (composed of 96% hydrocarbons, 3% lipids, and 1% proteins, in addition to potassium, magnesium, and copper), non-rubber components (formed by luteoids and Frey-Wyssling particles) and whey (composed by proteins, sugars, fatty acids, alcohols, and minerals).⁴ Its biomembrane, derived from a non-traditional method of vulcanization, is considered thin, elastic, and porous, participates as a physical barrier against infectious agents, in angiogenesis⁵ cell adhesion and extracellular matrix production² which has led to its use as a dressing and as a vascular prosthesis.⁶

In terms of global public health promotion, NRL has been pivotal through economically viable biomedical devices, enhancing access to medical technologies in developing countries. Latex-derived products, such as condoms, are vital in primary prevention, significantly reducing sexually transmitted infections (STIs) and supporting family planning efforts. Their availability has a direct impact on reducing HIV transmission and promoting reproductive autonomy. In hospital settings, latex devices like gloves and personal protective equipment (PPE) are essential in biosafety protocols, protecting healthcare professionals and preventing cross-infections, thereby ensuring health safety in healthcare environments.

METHODOLOGY

This is an integrative literature review conducted using the following steps: 1 – Choice of topic and definition of the research question; 2 – Establishment of inclusion and exclusion criteria for studies; 3 – Definition of the information to be extracted from the selected articles; 4 – Evaluation of the papers included in the review; 5 – Interpretation of results; 6 - Presentation of the synthesis of knowledge.

For the formulation of the guiding question, the PICO strategy, an acronym in English, whose meaning corresponds to "patient/population/problem, intervention, comparison and outcome" was used. Thus, the words natural rubber latex were assigned to the letter P, to the letters I and C, these were not used in the research, and to the letter O, and the terms biomedical applications were used. Based on this strategy, the following guiding question was obtained: "What are the biomedical applications of natural rubber latex?"

The database search was performed on December 27, 2021. These covered the U.S. National Library of Medicine (PubMed), the Web of Science, Scopus, and the Virtual Health Library (VHL) portal. As health terminology, the expressions "Natural Rubber" and "Biomaterials" were used included in the Health Science Descriptors (DeCS) and in the Medical SubjectHeadings (MeSH). As a Boolean operator, the English word AND was adopted.

The search was conducted by two researchers, who standardized the sequence of use of descriptors and crosses in each database, after which they proceeded with the comparison of results. To ensure a broad search, the databases were accessed through the periodic portal of the Coordination for the Improvement of Higher Education Personnel (CAPES), recognized by the Federal University of Ceará (UFC).

For the selection of publications, the following inclusion criteria were adopted: articles available in full, in Portuguese, English, or Spanish, published in the last six years (from 2015 to 2021), whose approach involved the use of NRL, obtained from *Hevea brasiliensis*, in biomedical application. As for the exclusion criteria, review studies were suppressed. To systematize this process, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was chosen.⁷ Two independent reviewers conducted the selection process, with the participation of a third researcher to resolve any conflicts.

For the extraction and synthesis of information, the instrument was used.⁶ Thus, the following variables were worked on: article coding, database, authors, year and country of publication; periodical; kind of study; level of evidence; main results, and biomedical application.

The assessment of the level of scientific evidence followed the classification which seven levels: 1 - Systematic review and meta-analysis, randomized controlled clinical trials or systematic reviews of randomized controlled clinical trials; 2 - Controlled and randomized trials; 3 - Cohort studies; 4 - Case-control studies; 5 - Report of cases/series of cases; 6 - Expert opinion/letters; 7 - Animal research / *in vitro* study (basic scientific studies).⁸

For the evaluation of the biomedical application, the studies were classified, according to the authors, into five categories, namely: 1 – Studies that used NRL as a matrix for releasing drugs/products; 2 – Studies that used NRL as a topical dressing; 3 – Studies that used NRL in the production of biomedical material; 4 – Studies that used NRL in tissue engineering; 5 – Studies that used NRL as a transdermal patch.

RESULTS

The search strategy identified 350 publications, of which 69 were excluded due to duplicity. After reading the title and abstract, 171 papers were excluded. Of the 110 selected for full analysis, 87 were excluded because they were reviews or did not address the research question. Thus, 23 studies composed the review (Figure 1).

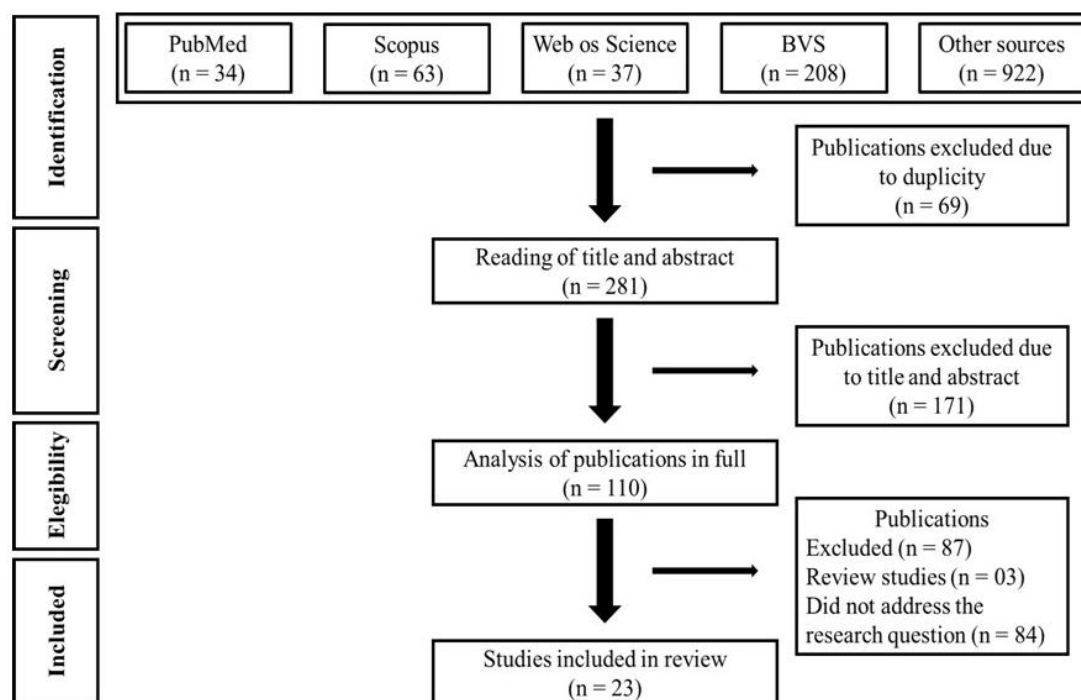


Figure 1 - Flowchart of article selection in databases adapted from Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA).

According to Table 1, of the 23 studies included, 43.47% (n = 10) were included in the Scopus database, 34.78% (n = 8) had been published in 2018 and 73.91% (n = 17) were developed in Brazil. As for the journal, 8.69% (n = 2) of the articles were published in the International Journal 'Journal of Polymeric Materials and Polymeric Biomaterials', equal to that of the 'Journal of Biomaterials Science', Polymer Edition. Regarding the type of publication and level of evidence, 95.65% (n = 22) of the studies had animal / *in vitro* as the type of study, a number equal to those with the level of evidence 7.

Table 1 - Characterization of publications included in the review, according to database, author, year of publication, country, journal, type of study, and level of evidence. Fortaleza, state of Ceará, Brasil, 2021.

Nº	Database	Author, Year	Country	Journal	Type of Study	LE*
01	Scopus	Almeida et al., 2020 ⁹	Brazil	Applied Surface Science	Animal study / <i>in vitro</i>	7
02	Web of Science	Gemeinder et al., 2020 ¹⁰	Brazil	Journal of Biomaterials Science	Animal study / <i>in vitro</i>	7
03	BVS	Barros et al., 2019 ¹¹	Brazil	Skin Research and Technology	Animal study / <i>in vitro</i>	7
04	Scopus	Garms et al., 2019 ¹²	Brazil	Applied Microbiology and Biotechnology	Animal study / <i>in vitro</i>	7
05	BVS	Krupp et al., 2019 ¹³	Brazil	International Journal of Biological Macromolecules	Animal study / <i>in vitro</i>	7

06	Scopus	Barros et al., 2018 ¹⁴	Brazil	Biomedical Physics & Engineering Express	Animal study / <i>in vitro</i>	7
07	BVS	George et al., 2018 ¹⁵	India	Scientific Reports	Animal study / <i>in vitro</i>	7
08	Web of Science	Guerra et al., 2018 ¹⁶	Brazil	Journal of Polymer Research	Animal study / <i>in vitro</i>	7
09	Pubmed	Miranda et al., 2018 ¹⁷	Brazil	Amino Acids	Animal study / <i>in vitro</i>	7
10	Scopus	Moopayuk; Tangboriboon, 2018 ¹⁸	Thailand	Key Engineering Materials	Animal study / <i>in vitro</i>	7
11	Web of Science	Morise et al., 2018 ¹⁹	Brazil	International Journal of Polymeric Materials and Polymeric Biomaterials	Controlled and randomized test	2
12	Pubmed	Suteewong et al., 2018 ²⁰	Thailand	Colloids and Surfaces B: Biointerfaces	Animal study / <i>in vitro</i>	7
13	Scopus	Barros et al., 2017 ²¹	Brazil	International Journal of Polymeric Materials and Polymeric Biomaterials	Animal study / <i>in vitro</i>	7
14	Web of Science	Floriano et al., 2018 ²²	Brazil	Journal of Polymers and the Environment	Animal study / <i>in vitro</i>	7
15	Web of Science	Garms et al., 2017 ²³	Brazil	British Journal of Pharmaceutical Research	Animal study / <i>in vitro</i>	7
16	Pubmed	Miranda et al., 2017 ²⁴	Brazil	Journal of Biomaterials Science, Polymer Edition	Animal study / <i>in vitro</i>	7
17	Scopus	Watthanaphanit; Rujiravanit, 2017 ²⁵	Thailand	International Journal of Biological Macromolecules	Animal study / <i>in vitro</i>	7
18	Web of Science	Barros et al., 2016 ²⁶	Brazil	International Journal of Peptide Research and Therapeutics	Animal study / <i>in vitro</i>	7
19	Scopus	Lee et al., 2016 ²⁷	Malaysia	Journal of Applied Polymer Science	Animal study / <i>in vitro</i>	7
20	Scopus	Borges et al., 2015 ²⁸	Brazil	Journal of Biomaterials Science, Polymer Edition	Animal study / <i>in vitro</i>	7
21	Scopus	Macartto et al., 2021 ²⁹	Brazil	Journal of Applied Polymer Science	Animal study / <i>in vitro</i>	7
22	Scopus	Miranda et al., 2021 ³⁰	Germany	Polymer Bulletin	Animal study / <i>in vitro</i>	7
23	Pubmed	Lima et al., 2021 ⁶	Brazil	Journal of Applied Biomaterials and Functional Materials	Animal study / <i>in vitro</i>	7

*Level of Evidence

When evaluating the objectives/biomedical application of the studies, these, in general, involved the incorporation of drugs/products to the NRL membrane, ranging from antimicrobials (especially antibiotics) and anti-inflammatories to vegetable oils, hormones, and natural/synthetic products (such as propolis, poly(isoprene), chitosan and [W⁶] haline a1), which aimed to evaluate the effect of this incorporation on phenomena such as antimicrobial activity, analgesia, tissue repair, the release of breast milk and reduction of adverse events (Table 2).

Regarding the results of drug/product incorporation into the LBN membrane, the publications indicated in general, that the drugs/products were likely to be incorporated into the NRL membrane, depending on the pore density and size, without inducing structural changes and without showing significant interaction with the membrane. Typically, the release occurred initially quickly, followed by a slower process.

The authors also reported that the incorporation did not demonstrate hemolytic and toxic activity, in addition to presenting antibiotic action against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Burkholderialata*. Furthermore, the aggregation of drugs/products to the NRL membrane promoted the formation of granulation tissue, angiogenesis, and collagen synthesis.

Specifically, the studies also showed greater porosity, elongation, wettability, hydrophilicity, and lower tensile strength in NRL membranes loaded with glycerol or propolis.

Table 2 - Characterization of publications included in the review, according to objective, main results, and biomedical application. Fortaleza, state of Ceará, Brasil, 2021.

No	Objective	Main Results	Biomedical Application (Drug/Product)
01	To report the production of micropores in an NRL membrane by femtosecond laser micromachining. To evaluate the release of ciprofloxacin charged on this membrane	Femtosecond laser preserved membrane properties while enabling controlled drug release, with higher porosity leading to increased drug delivery and final concentration.	Drug/Product Release Matrix (Ciprofloxacin)
02	To incorporate gentamicin sulfate into NRL biomembranes to reduce drug side effects. Evaluate the antibiotic properties of this incorporated biomembrane against <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> present in infected skin ulcers	Gentamicin sulfate improved biomembrane performance, maintained antibacterial activity, and showed no toxicity in <i>C. elegans</i> , though it reduced larval mobility.	Dressings for bacterially infected skin ulcers (Gentamicin Sulfate)
03	To develop and characterize a low-cost compound, with repairing and moisturizing properties, for pain relief and healing of nipple fissures caused by breastfeeding	The glycerol-loaded NRL membrane increased porosity, elongation, and wettability but reduced tensile strength. It was non-toxic when diluted and showed no hemolytic effects.	Dressings for nipple fissures (Glycerol)
04	To develop a polymeric device for the treatment of infections and tissue repair. To explore the effectiveness of this biomaterial in strains of <i>S. aureus</i> , <i>S. epidermidis</i> , <i>Pseudomonas aeruginosa</i> , and <i>E. coli</i> for the treatment of infected chronic wounds	The moxifloxacin-loaded NRL membrane showed no cytotoxicity and was effective against <i>S. aureus</i> , <i>S. epidermidis</i> , <i>P. aeruginosa</i> , and <i>E. coli</i> , unlike the unloaded NRL membrane, which lacked antibiotic activity.	Dressings for infected chronic wounds (Moxifloxacin)
05	To evaluate the effects of the NRL membrane associated with the aqueous extract of propolis on healing in a burn model with rats	The NRL membrane with propolis improved hydrophilicity, porosity, lesion retraction, and keratinocyte organization, enhancing granulation, angiogenesis, and collagen synthesis.	Dressings for burns (Propolis)

No	Objective	Main Results	Biomedical Application (Drug/Product)
06	To develop an NRL membrane loaded with antioxidant <i>Sarasinula marginata</i> extract. To evaluate its activity <i>in vitro</i> , comparing two spectrometric techniques	FTIR analysis confirmed successful incorporation of <i>S. marginata</i> extract into the NRL with controlled release. The DPPH evaluation showed that the antioxidant activity of the extract was preserved after incorporation.	Drug/Product Release Matrix (<i>Sarasinula Marginata</i>)
07	To verify if graphene associated with NRL produces film nanocomposites capable of being tensile-resistant, extending, and biocompatible	The incorporation of graphene into NRL created nanocomposites with biocompatibility, low cytotoxicity, no skin irritability, and good tensile and elongation resistance.	Production of biomedical materials (gloves, catheters, and condoms) (Graphene)
08	To characterize chemically the change in the structure of poly(isoprene) (PI) from NRL. To evaluate its effect in the preparation of poly (lactic-co-glycolic acid) (PLGA) blends to improve chemical compatibility with Cellprene ^{®(e)} (PLGA/PI blend) and increase its applications in Tissue Engineering	The PI epoxidation increased its polarity compared to NRL. The PLGA/PI epoxidized blends were partially miscible, biocompatible, and suitable for Soft Tissue Engineering. Epoxidized PLGA/PI showed better cell proliferation and adhesion than PLGA/PI.	Feasibility for application in Tissue Engineering [Poly(isoprene)]
09	To evaluate the incorporation and release of peptides using a latex biomembrane carrier	SEM ^(f) analysis showed that part of the peptide [W6]Hylin a1 was retained on the NRL biomembrane surface. Enzymatic degradation of the peptide by latex proteases was also observed.	Drug/product release matrix ([W ⁶]Hylin a1)
10	To evaluate whether the mangosteen seed, associated with the NRL plaster, can be used as a drug delivery system, including for pain relief in patients with osteoarthritis	Mangosteen seed powder, rich in lipids, had a 41.50°C degradation temperature. In NRL plaster, it gave water and alcohol contact angles of 80.8° and 0.0°, maintaining similar mechanical properties.	Adhesive for drug/product delivery (Mangosteen Seed Powder)
11	To develop a Transdermal Drug Delivery System using NRL membranes loaded with scopolamine butylbromide for future transdermal treatment of sialorrhea	Scopolamine butylbromide showed a 32% fast release in 24h and 65.3% slower release in 72h from the NRL membrane. It increased FTIR band intensity, improved wettability, and showed no hemolytic effect.	Drug/Product Release Matrix (Scopolamine Butylbromide)
12	To develop a double antibacterial system, containing chitosan and silver nanoparticles, capable of being used with rigid substrates (polymethylmethacrylate) in NRL film	Silver and chitosan nanoparticles on the NRL film showed limited antimicrobial activity and no roughness change. Adding them to polymethylmethacrylate-enhanced NRL improved roughness and antibacterial activity.	Drug/Product Release Matrix (Chitosan, silver nanoparticles, and polymethylmethacrylate)
13	To develop an NRL membrane loaded with desmopressin. To characterize the release of this peptide <i>in vitro</i> , aiming	SEM showed crystals of desmopressin on the NRL membrane. FTIR indicated non-covalent interactions. Peptide release was 35% in 2 hours and 60% in 96 hours, with no hemolytic activity observed.	Drug/Product Release Matrix (Desmopressin)

No	Objective	Main Results	Biomedical Application (Drug/Product)
	for its use in the treatment of enuresis		
14	To develop a transdermal delivery system for ketoprofen incorporated into the NRL membrane	SEM confirmed ketoprofen on the NRL membrane surface with solid aggregates. FTIR showed no significant interaction. The drug reduced elongation but maintained tensile strength, with no hemolytic effect.	Drug/Product Release Matrix (Ketoprofen)
15	To develop a ciprofloxacin-loaded NRL membrane to accelerate tissue repair and control wound infection. To characterize the biomaterial regarding its structure, morphology, resistance, and microbiological activity	SEM showed ciprofloxacin crystals on the NRL membrane, with no crystallinity confirmed by X-ray diffraction. FTIR indicated drug stability, and thermogravimetric analysis revealed altered degradation. The ciprofloxacin-loaded membrane completely inhibited <i>Burkholderialata</i> .	Dressings for infected wounds (Ciprofloxacin)
16	To develop a method to produce NRL membranes via lyophilization, allowing the control of membrane porosity, through the addition of different volumes of water and the release of bovine serum albumin	SEM showed a direct relationship between pore number and water volume in NRL membrane formation. Larger pores increased water vapor permeability and bovine serum albumin release. The membrane showed no hemolytic activity or cytotoxicity, regardless of pore presence.	Dressings for wounds (NRL membrane by lyophilization)
17	To produce NRL film associated with sericin and mustache chitin as an alternative product for the treatment of wounds. To develop new elastic dressings applicable for wounds where pressure is required to “cushion” the wound	SEM showed small protrusions on the film surface due to increased chitin. The membrane had higher stress at rupture with more sericin, reduced by chitin. Water absorption increased with sericin but not chitin. A small amount of chitin favored sericin release, and cell viability was highest with 20% sericin.	Elastic dressings for wound care (Sericin and mustache chitin)
18	To develop a new oxytocin release system in NRL membrane, aiming its use as a dermal adhesive for the release of breast milk	The NRL membrane absorbed 1.08g of water per gram in 16 hours. SEM showed oxytocin aggregates on the surface, and FTIR revealed no covalent binding. The release was initially fast, then slower, with no hemolytic activity at 100 µg/mL.	Drug/Product Release Matrix (Oxytocin)
19	To describe the preparation and characterization of NRL plasticized with vegetable oil emulsions, aiming at the effectiveness of this film in reducing the survival of <i>E. coli</i> and <i>S. aureus</i>	Vegetable oil microemulsions (palm kernel, coconut, and soybean) increased NRL particle size by 13.4% to 17.0%, reduced mechanical properties, and increased swelling. The NRL-oil combination showed antimicrobial activity against <i>S. aureus</i> , but not against <i>E. coli</i> .	Dressing for infected wounds (Palm Kernel, Coconut, and Soy Oil)
20	To create a compound capable of improving the properties of calcium phosphate and NRL for biomedical applications	SEM ^(f) showed calcium phosphate particles on the NRL biomembrane surface. The biomembrane did not induce hemolytic activity up to a concentration of 0.125 mg/mL, regardless of calcium phosphate presence.	Drug/Product Release Matrix (Calcium Phosphate)
21	To produce polylactic acid structures, with two different geometries in 3D, coated with NRL, aiming at biomedical applications	Polylactic acid with NRL showed improved leveling, uniformity, and unchanged pore diameter. FTIR indicated no chemical reaction, and no changes in compression or hemolytic activity were observed.	3D structures for cell cultivation

No	Objective	Main Results	Biomedical Application (Drug/Product)
22	To evaluate the effect of metronidazole and silver nanoparticles incorporated into the NRL membrane as carriers in a controlled release system	SEM showed silver nanoparticles and metronidazole crystals on the NRL membrane. Release was faster from the surface and slower from within. No chemical changes or hemolytic activity were observed.	Dressing for infected wounds (Metronidazole and silver nanoparticles)
23	To incorporate ibuprofen into the NRL membrane, aiming at the production of a new biocompatible adhesive for the treatment of inflammatory processes, capable of reducing adverse effects	Ibuprofen reduced NRL elasticity, increased deformation by 33%, and tensile strength by 43%. It released faster in a basic medium and showed no hemolytic activity.	Adhesive for drug administration (Ibuprofen)

^(a)FTIR- Fourier transform infrared spectroscopy; ^(b)ATR- Total Attenuated Reflection; ^(c)DPPH -Spectrophotometric assay; ^(d)EPR - Electronic Paramagnetic Resonance Assay; ^(e)Cellprene® - blend patented by the Federal University of Rio Grande do Sul; ^(f)SEM - Scanning Electron Microscopy; ^(g)AFM - Atomic Force Microscopy.

DISCUSSION

This integrative review made it possible to gather literature on the biomedical applications of NRL, derived from *H. brasiliensis*, a rubber tree native to the Amazon rainforest and the main source of natural rubber. In particular, this work sought to explain the general findings obtained in studies published in scientifically relevant databases, which may contribute to the development of research aimed at clinical practice regarding the use of NRL membranes and the different physical, chemical, and biological mechanisms triggered by their use.

When evaluating the databases of the articles included, the greater number of publications in Scopus may be a reflection of the importance of the theme addressed here. Furthermore, Scopus represents one of the largest databases of bibliographic abstracts and curated citations.³¹

Regarding the year of the works, the highlight for 2018 may be a reflection of the prioritization, in the period from 2019 to 2021, of research focused on the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and Coronavirus Disease - 19 (COVID- 19). It can also be assumed that it resulted from the limited financial support instituted by the Federal Government for research, experienced in recent years.

About the country where the research was conducted, the predominance of articles from Brazil can be understood if we admit that *H. brasiliensis* is a botanical species native to the Amazon, having, as the only source of its product (natural rubber), Brazil, until the mid-twentieth century.⁴

Concerning the journal, the fact that all studies were published in international journals, especially in the International Journal of Polymeric Materials and Polymeric Biomaterials (regarded as the official publication of the International Society of Biomedical Polymers and Polymeric Biomaterials) and Journal of Biomaterials Science Polymer Edition (a magazine that publishes relevant works in the context of the properties of polymeric biomaterials and their interaction with living organisms, particularly at the molecular and cellular level), was surprising, given that most of them were developed in Brazil.

This data may be an indication that national researchers are interested in international journals, enabling greater visualization and reach of information, collaborating with the internationalization of Brazilian science. Added to this, there may be greater international interest in Brazilian biodiversity.

As regards the type of study and level of evidence of publications, the fact that most of them involved animal research/*in vitro* study and the strength of evidence 7 can be justified by animal research allowing the investigation of the effect of a substance/product on the whole organism.⁶ In addition, this type of study provides clarification of issues related to physiological and pathological processes, with repercussions in clinical practice.

For the *in vitro* study, its use by most of the articles contained in this review can be based on the fact that this type of research can obtain important information for the human being when making use of the cultivation of cells, tissues, and organs in an environment external to the organism. It is noteworthy that, despite the reduced strength of scientific evidence, animal or *in vitro* research is recognized as crucial for the advancement of Medicine and continuous support for Morphofunctional Sciences.

When analyzing the objective and medical applicability of the studies included, the preponderance of the use of NRL as a drug/product release matrix may be associated with the growing interest of the pharmaceutical sector in innovating and investigating delivery systems capable of improving therapeutic effects, minimizing side effects, regulate the release and extend the duration of drugs.³² Such interest can be provided by the NRL membrane being a potent carrier system associated with its biocompatibility, low cost, ease of manipulation, and induction of angiogenesis and cell adhesion.

Specifically for the incorporation of antibiotics into the NRL membrane, as pointed out in the articles of this review, this conduct is justified because they are one of the most prescribed groups of drugs³³ and are important in controlling infections. In addition, it is possible to alter the kinetics and time of the release of these drugs by simply changing the morphology of this membrane.³⁴

For anti-inflammatory drugs, the interest in integrating them into the membrane may be based on their high worldwide consumption, associated with the prospect of reducing their systemic adverse effects, including serious ones, provided by transdermal delivery systems. Regarding vegetable oils, their study associated with the NRL membrane can be understood if it is admitted that these renewable and sustainable materials are capable of acting as natural rubber plasticizers, reducing their viscosity⁴ and cost. Also, they can improve the processing properties of this rubber and increase flexibility at low temperatures.

Concerning the hormone incorporation into the NRL membrane, this purpose is understandable if one observes the importance of hormone replacement therapy in menopause and andropause situations, particularly using formulations such as patches. These, when sensitive to pressure and incorporated into natural rubber, are widely adopted due to the latter's properties of crystallizing under stretching.³⁵

Regarding the natural/synthetic products associated with the NRL membrane, the use of propolis can be understood if one considers that this natural substance stands out as an additional material for dressings, presenting antibacterial, non-hepatotoxic, and immunogenic effects. Furthermore, it is regenerative and anti-inflammatory.

Namely, the incorporation of propolis to the NRL membrane provides this flexibility, porosity, and hydrophilicity, properties that can favor angiogenesis, formation of granulation tissue, and organization of a protective barrier to facilitate exudate drainage and greater adherence of the membrane to the injury and acceleration of cell multiplication.

For chitosan, its association with the NRL membrane may be related to its use as a biopolymer in the treatment of wounds and drug delivery. This applicability is based on its properties of biocompatibility, biodegradability, and similarity with the extracellular matrix, in addition to promoting healing.⁶

Specifically, in the paper included here, chitosan was employed to stabilize negatively charged poly(methyl methacrylate) latex particles.³⁶ In addition, as the objective of the study was to develop a dual antibacterial system, capable of being used with rigid substrates (polymethylmethacrylate) in NRL film, chitosan was also adopted for presenting antimicrobial activity.³⁷

Regarding poly(isoprene), its applicability in studies is justified by the fact that natural rubber is an isoprene polymer, giving it simplicity in its composition and elasticity, despite a high average molecular mass.⁴ About the [W⁶] hilina a1, a peptide compound modified from hilina a1, an antimicrobial peptide derived from the frog *Hypsiboas Albopunctatus*, its incorporation into the NRL membrane is based on the fact that this compound has antimicrobial activity, favoring this effect in this association. Indeed, this system can act as a release matrix for different molecules³⁸ in addition to contributing to tissue repair.

When investigating the results presented by the publications addressed in this work, the fact that they focused on the incorporation of drugs/products into the NRL membrane highlights the desire to use this latex as a matrix for a controlled drug release system. In particular, this type of system allows for a longer-lasting action of the active ingredient, greater safety, adherence, and efficacy, in addition to a lower frequency of administration and toxic effects.

In this context, it is worth noting that the presence of the drug/product on the surface of the membrane is associated with a more accelerated release into the environment, a phenomenon known as rapid release. This involves an almost spontaneous availability of a part of the substance to the external environment.⁶ The slower release phase is characterized by the location of the drug/product inside the membrane.

Regarding the interference of porosity on the incorporation and release of drugs/products portrayed in the publications of this review, it was noticeable in the article by which stated that a greater ciprofloxacin release occurred in NRL membrane with higher pore density.³¹

Although this phenomenon occurred in NRL membrane subjected to femtosecond laser micromachining, this increase in porosity and, consequently, a greater release of the drug/product³⁹ could result from the addition of water during the process of production of this membrane, including an increase in vapor permeability to this molecule. Specifically, this strategy is necessary to alleviate allergic reactions and cytotoxicity triggered by the NRL membrane, obtained by conventional methods.

Regarding the absence of structural alterations and significant interaction between the drugs/products and the membrane, regardless of the technique used to incorporate these drugs/products into it, these findings confirm its use as a drug delivery system, providing their availability for the medium, without interfering in its composition.

This result is particularly surprising if you consider that NRL is made up of isoprene, a very reactive compound. However, this lack of structural alteration and considerable connection between the drugs/products and the NRL membrane can be understood when observing that, in addition to the presence of water, poly(cis-1,4-isoprene) and poly(trans- 1,4-isoprene) and α and ω chain terminal groups, this type of latex contains carbohydrates, proteins and lipids^{2,32} the last two being responsible for colloidal stability.

Still, in organizational terms, although controversial, it is admitted that the NRL is formed by a hydrophobic core surrounded by a mixed layer, composed of 84% proteins and 16% phospholipids.³² In

this structure, repulsive electrostatic forces, steric repulsive forces, solvation forces, and attractive Van der Waals forces are expected to act.⁴⁰

Concerning the absence of hemolytic activity when drugs/products are incorporated into the NRL membrane, this data highlights the safety of using this system, including in humans, especially considering that this type of test is directly related to the toxicity of substances.⁴¹ Notably, this type of analysis is based on the similarity of the erythrocyte membrane with the membrane of other cells, in addition to the ease of access to blood and isolation of this cell type.

Similar to the assessment of hemolytic activity, the absence of toxicity when associating drugs/products with the membrane reinforces the safety of the process, particularly as it is a mandatory step in the investigation of new molecules/drugs. Furthermore, through this type of analysis, the scope of the therapeutic action can be defined.

Regarding the antibiotic action presented by the drugs/products incorporated into the NRL membrane, this data supports the fact that the antimicrobials associated with the membrane are released into the environment and exert their effect, which can be amplified by the components of *H brasiliensis*, represented by proteins such as hevein, chitinase, β -1,3-glucanase and glucosidase, and ammonia.³²

Concerning the angiogenic property of the drugs/products incorporated into the membrane, this action can be perceived if we admit that this membrane is capable of releasing a substance similar to the Vascular Endothelial Growth Factor, inducing the restitution of arteries and veins.³²

For the formation of granulation tissue and collagen synthesis reported by the articles in this review, it can be justified by the NRL membrane stimulating the production of Transforming Growth Factor- β 1 (TGF- β 1)⁴² a cytokine responsible for cell migration and extracellular matrix synthesis in the repair process, as well as for fibroblast proliferation.

Regarding the greater porosity, hydrophilicity, and wettability exhibited by propolis associated with the NRL membrane, this result had already been observed.⁴³ The increase in porosity may be due to the presence of pores in the membrane since the propolis film is smooth and smooth. Regarding the greater hydrophilicity and wettability, these phenomena may result from the fact that propolis is hydrophilic, decreasing the contact angle between the liquid and the surface.⁴³

For the glycerol, used with the membrane to favor hydration in the nipple region³⁹ the elongation provided by its incorporation into the NRL membrane may be related to the action of this plasticizer between the polymer chains, reducing the interactions and increasing mobility.⁴⁴ As for the lower tensile strength, it may be associated with the concentration of glycerol used, which can be corroborated with what was observed.⁴⁵ According to the authors, the biodegradable film of chitosan incorporated with glycerol supported a higher tensile stress when at a lower concentration of glycerol.

In terms of practical implications, this study demonstrated that incorporating various drugs and products, such as antibiotics, anti-inflammatories, and natural/synthetic compounds, into NRL membrane can effectively enhance their biomedical applications, including antimicrobial activity, tissue repair, and reduction of adverse events. The substances were successfully integrated without causing structural changes or significant interactions with the NRL membrane, with release profiles showing an initial rapid release followed by a slower phase. The incorporation exhibited no hemolytic or toxic activity and showed antibacterial effects against multiple strains. Furthermore, it promotes granulation tissue formation, angiogenesis, and collagen synthesis, although membranes with glycerol or propolis had increased porosity, elongation, wettability, and hydrophilicity but lower tensile strength.

As limitations of this review, we mention, as the most relevant, the lack of national and international publications capable of supporting the discussion of certain results reported here,

especially regarding the physical, chemical, and molecular interaction between drugs/products of NRL release and membrane, as well as the mechanisms involved in the non-toxicity of this membrane and its biological effects.

CONCLUSION

Based on the presented results, it can be concluded that NRL demonstrates significant potential for biomedical applications, particularly regarding the incorporation and controlled release of drugs and products. The integrative review showed that the effectiveness of this incorporation is intrinsically related to the structural characteristics of the membrane, such as density and pore size, while maintaining its structural integrity during the process. It is also noteworthy that, despite the rapid initial release of the incorporated components, the material demonstrated biocompatibility with different cell types, showing no significant adverse effects, which reinforces its potential as a promising biomaterial for various therapeutic applications.

Based on the presented work, several research gaps and future directions can be identified. Key limitations include the restricted search period and focus primarily on drug incorporation studies, while notable gaps encompass the lack of longitudinal studies, insufficient comparisons with other biomaterials, and limited investigation of cost-effectiveness. Future research should focus on conducting randomized clinical trials, exploring new techniques for NRL structure modification, investigating combinations with other biomaterials, and expanding into regenerative medicine applications, while also addressing the economic feasibility of large-scale production.

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