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REVIEW ARTICLE

Latex and natural rubber: recent advances for biomedical applications

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Abstract

Recently, latex (NRL) and natural rubber (NR) from *Hevea brasiliensis* have emerged as promising biomaterials from renewable sources for biomedical applications. Although some attempts at commercial applications have been made, there is a need to comprehensively document the state-of-the-art of these biopolymers for biomedical applications and regenerative medicine. Here we present the recent advances in the development of NRL and NR as biomedical materials with potential properties including biocompatibility and biodegradability. Due to the angiogenic properties of NRL and NR, well-defined functional materials can be used for drug delivery systems (oral/transdermal), scaffolds for skin and bone regeneration, and dressings for wound healing. The incorporation of drugs, nanoparticles, cells, and others into NRL and NR polymer chains offers a wide range of applications such as dressings with antimicrobial activity and sustained release systems. Concluding remarks on the growth of these biomaterials for biomedical applications and regenerative medicine were discussed.

Keywords: *drug delivery system, Hevea brasiliensis, scaffolds, tissue repair, wound dressing.*

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1. Introduction

Natural Rubber Latex (NRL), produced by the Brazilian rubber tree *Hevea brasiliensis*, is a colloidal system containing approximately 50 wt.% water, 30-45 wt.% rubber particles (mainly cis-1,4-polyisoprene), and 4-5 wt.% nonrubber constituents, including proteins, lipids, and carbohydrates[1-4]. Natural Rubber (NR), obtained from NRL, is a polymeric substance of high molecular weight and has viscoelastic properties, which makes it ideal for various applications, in which biomedical applications stand out[3-8].

Recent work has shown that NRL and NR are bioactive materials that promote cell adhesion, extracellular matrix formation, and accelerating tissue repair due to increased angiogenesis at the site of injury[9,10]. NRL and NR polymers present biocompatibility, and angiogenic properties that induce tissue healing, high elasticity, flexibility, and mechanical strength[6,7,11-14]. A range of biomedical devices based on NRL and NR have been recently developed to accelerate tissue repair, including wound dressings, cellular scaffolds, as well as components of sustained drug delivery systems and transdermal drug delivery patches[8,11,12] (Figure 1).

Although significant progress has been made in utilizing NRL and NR as functional biomaterials, there is a need to comprehensively document these developments for biomedical applications and regenerative medicine. This review aims to study and discuss the advances in the field of NR and NRL biopolymers and to foster a better conception of how these polymers have evolved as a field of significance in biomedicine. A summary of the biodegradability and biocompatibility of NRL and NR is first presented. Next, the application as a biomedical device and the incorporation of additives are discussed. Finally, the review presents the conclusions and remarks for the future growth of NRL and NR biomaterials for biomedical applications and regenerative medicine.

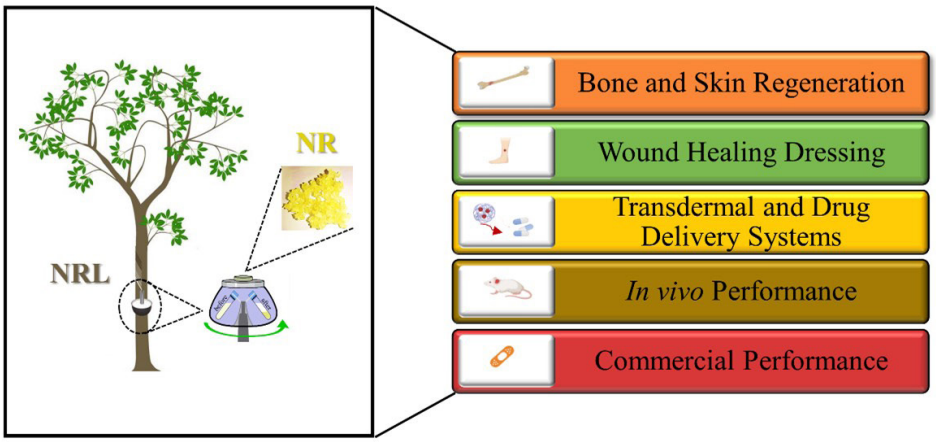

Figure 1. Recent advances for biomedical applications of NRL and NR.

2. Biocompatibility and Biodegradability

The most important characteristics of biopolymers with potential application in the biomedical field refer to their biocompatibility and biodegradability, making them promising alternative eco-friendly resources to non-degradable synthetic polymers, which are common in short-term applications in biomedicine[15,16].

Biocompatibility describes the ability of a biomaterial to perform its intended purpose in medical therapy without causing harmful effects on the body[17]. The material is usually analyzed by *in vitro* cell culture studies, including cytotoxicity tests, biochemical measurements of cell activity, and evaluation of cell proliferation, growth, and morphology[18]. *In vitro* cytotoxicity analysis is standardized and regulated by a series of standards e.g. 'ISO 10993: Biological Evaluation of Medical Devices' that evaluate the materials intended for the manufacture of devices for biomedical applications. The *in vitro* evaluation has the advantage of limiting the experimental variables, and it is easy and fast to obtain meaningful data. When the non-toxicity of the material is proven, animal studies must be performed[19-21].

Several studies have already been performed regarding the biocompatibility of NRL and NR. According to the literature, the biocompatibility of NRL is well established[3,7,13,22,23]. However, there are still some aspects to be considered for this property to become even more satisfactory, such as a safer collection method and adequate processing[8]. Both factors can directly influence the biocompatibility of NRL and NR, interfering in their application. Floriano et al. observed that latex membranes in contact with ammonia during collection showed cytotoxic and genotoxic effects on cultures of NIH3T3 fibroblasts. All clones showed increased cell viability compared to the sample without ammonia[22]. Twelve types of commercial NRL gloves were analyzed and showed that residual chemicals are the main cause of poor biocompatibility. Experiments indicated that solvent washing can effectively remove residues from medical devices[24]. In return, NRL membranes showed no cytotoxicity and allowed adhesion, proliferation, and extracellular matrix deposition for MC3T3-E1 osteoblasts[3,23].

Besides biocompatibility, biodegradability is another fundamental material property for biomedical materials. Biodegradable polymers are characterized by being broken down into biologically acceptable molecules through enzyme catalysis, involving hydrolysis or oxidation[25]. The biodegradability of NR has been widely studied due to the growing indiscriminate use of its by-products e.g. thousands of units of disposable gloves and NRL condoms that are discarded in nature, as well as the difficulties encountered in the reuse of these materials. For instance, the demand for personal protective equipment related to the circulation of the SARS-CoV-2 virus has increased since 2020. Given the limited space in landfills, the high cost of incineration, and the high potential risk to health and the environment, the studies on the biodegradability of NR become fundamental[26-28].

The first studies developed on the degradation of NR by microorganisms started more than 100 years ago, but currently there is still a shortage of biotechnological applications[26]. Some studies reporting the use of microorganisms, enzymes, and composting in the biodegradation of NR are reported in the Supplementary Material (Table S1). When evaluating the degradation of NR in the presence of *Penicillium* and *Aspergillus*, Tsuchii et al. verified a 32% weight loss in 30 days[29]. Most NRL and NR biomedical materials are still not degradable or do not present absorption by the body due to slow microbiological biodegradation, making it necessary to remove the material after implantation[8]. The blending with other compounds provides higher levels of degradation of NR, for instance, NR blended with cellulose and sodium alginate showed a mass loss of 50% after 56 days[30]. The association of NR and crosslinked nanocellulose also showed more promising degradation results by using *Eudrilus eugeniae*, in which about 60% weight loss was observed after 120 days[16].

Even when NRL and NR are combined with other biodegradable compounds, the problem remains. A possible solution to this fact would be deproteinization of the NRL

which makes the material safe to remain inside the body for long periods without the need of removal[22]. In addition, most of the studies concerning the biodegradation of NR are conducted on a laboratory scale. Another fact that deserves to be highlighted is the scarcity of studies involving the biodegradation of NR in biomedicine. There is still a need for the development of materials based on NRL and NR with a higher level of biodegradation with biomimetic characteristics, thus maintaining their structure and function for a longer time.

3. Application as a Biomedical Device

Among the various techniques used to produce biomedical materials from NRL and NR, the casting technique stands out for its simplicity of handling. Another technique that deserves to be highlighted, but has been little explored, is electrospinning, which can produce fibers with diameters ranging from micro- to nanoscale by controlling the process parameters. Other techniques show potential for processing NRL and NR, such as NRL protein extraction and blow spinning. Processing techniques including casting, spraying, dipping, electrospinning, among others (more information is found in the Supporting Material), result in different NRL and NR biomedical devices, which have been applied mostly as drug delivery systems and scaffolds for skin and bone regeneration, while the application for wound healing dressing and transdermal drug delivery system has been less investigated. Some *in vivo* tests were conducted, however, commercial application of NRL and NR as biomedical devices is very limited. The biomedical applications of NRL and NR are described below.

3.1 Drug delivery systems

Drug delivery systems are responsible for the body internally delivering a drug or active compound in the desired dose to a particular region of the human body, which can improve efficacy and safety by controlling release rate, time, and location[31,32]. This system development allows a more selective and precise release to a specific site and requires a lower dosage because the delivery is *in situ*, with more consistent absorption and a decrease in toxic metabolites[33].

Networks' formation by the isoprene chains works as a reservoir that allows the gradual release of compounds, highlighting its potential for drug delivery[11,34,35]. Using NR as a solid matrix for drug delivery systems is reported in several studies involving wound dressings[12,36,37]. Some studies have reported sustained-release provided by NRL and NR occurring through diffusion, which can be facilitated through fractures and pores on their surface with the 'burst release'[34,38,39]. Drug release kinetics can be altered by structure modifications of NRL and NR devices, such as porosity increase/decrease, increased drug incorporation into the bulk material or its surface, or into the shell[4]. Combining NRL or NR with drugs or bioactive compounds promotes the incorporation of new properties to the material, which can provide even more satisfactory results in biomedical applications 'optimization'. This incorporation is preferably done with NRL because it is a liquid suspension and provides greater miscibility of the compound when compared to incorporation in NR, which is a solid material.

Table 1 mentions some drugs and bioactive compounds that have been used in formulations with NRL and NR, including ciprofloxacin, propolis, and *Casearia sylvestris Swartz.* Ciprofloxacin is an antimicrobial agent that has antioxidant potential when incorporated into any dressing, promoting the acceleration of the healing process[43]. It has long been known that silver is highly toxic to microorganisms, showing strong biocidal effects on bacteria and fungi[57]. Propolis is also an antibacterial with relevant pro-activating characteristics[58], which presents great advantages over the most common antibacterial agents, standing out due to its high biocompatibility, antimicrobial power, and natural source origin[59,60]. Propolis is widely used in biomedical dressings, representing a strategy that goes beyond the prevention of injury infections, because it still has pro-healing characteristics, triggering the acceleration of the injury healing process. *Casearia sylvestris Swartz* is a Central and South American tree from which its leaves are used in the treatment of gastric diseases and also for antiophidic, anti-inflammatory, anti thermal, and wound healing purposes[61].

Extract of *Casearia sylvestris Sw.* and ciprofloxacin was incorporated into NR films preserving the properties of the substances since no chemical interaction between materials was observed[40]. The release rate of the extract was higher (~94%) than that of ciprofloxacin (~54%), both substances being adhered to the surface of porous NR films. With ciprofloxacin loading, the release of the drug was observed to be linearly proportional to the manufactured pore density[31].

Serjania marginata extract was incorporated into NR matrix, and 27% of the extract was released after 67 h preserving its antioxidant activity[39]. A sustained delivery system for metronidazole was developed from NRL, with control of metronidazole according to the polymerization temperature of the NRL matrix. Polymerization at -100 °C showed the best potential for metronidazole release, with approximately 77% of metronidazole being released after 310 h, i.e., release rate was slow[49].

These combinations provide the development of materials with antimicrobial, anti-fungal, and antioxidant activities, among other properties, that when associated with the biocompatibility of NRL and NR, demonstrate the great potential of these materials in biomedical applications. These materials reduce the cost of therapy, provide greater treatment efficacy, and improve the patient's quality of life. It is also worth highlighting the benefits of using NRL and NR in drug delivery systems due to their versatility and easy handling, being possible to modify their release kinetics according to the type of application.

3.2 Transdermal drug delivery systems

Transdermal Drug Delivery System (TDDS) is a painless, non-invasive drug delivery technique, where the drug is simply made available from a skin patch or other transdermal method/device, running through the skin layers until it reaches the systemic circulation, reaching the specific organs for the treatment. Even with the advances in TDDS and the discovery of delivery devices for drugs of

Table 1. Overview of drugs and active compounds added to NRL and NR applied to biomedicine, with respective concentrations and solvents.

Drug/active compound; concentration ($mg \cdot mL^{-1}$)	Solvent for drug/active compound impregnation	Reference
Bovine serum albumin; 2; 10	N/A; Deionized water	[4,37]
Casearia sylvestris; 0.25; 0.1; 1; N/A; 0.25	Ethanol; Ethanol; Ethanol; Ethanol and water; Ethanol	[12,36,40-42]
Ciprofloxacin; 3; 0.1; 10; 5; 0.01	N/A; Water; Water; Water; N/A	[31,40,43-45]
Diclofenac; 3	N/A	[11,38]
Fluconazole; 10	N/A	[46]
Hydroxyapatite; 1, 2 and 3	THF	[47]
Ketoprofen; 10	Ethanol and water	[34]
Metronidazole; 10	N/A	[48,49]
Propolis; 0.05; N/A; 0.05; 1, 2 and 3	Ethanol and water; Ethanol and water; Absolute ethyl alcohol and water; Absolute ethyl alcohol	[35,50-52]
Serjania marginata; 30	Ethanol and water	[39]
Silver; 0.1; 0.1; 679.5	Sodium borohydride; Deionized water; NRL diluted in water Mili Q	[53-55]
Stryphnodendron obovatum; 0.1 and 5	Ethanol and water	[56]

various origins (lipophilic, hydrophilic, and amphiphilic), dosage levels are still not competitive when compared to traditional delivery options[62,63]. This type of system can be developed using both synthetic and natural polymers as matrices including NR.

To minimize common events triggered by this type of drug delivery, a TDDS of ketoprofen was developed by its incorporation in NR biomembranes. In this study, the chemical interaction of the drug with the membrane was not verified and a drug release of 60% was observed due to the portion of ketoprofen present on membrane surface. The researchers concluded that this system is promising for drug administration, minimizing adverse effects caused by high dosages[34]. TDDS composed of a deproteinized NR matrix, hydroxypropyl methylcellulose, and dibutyl phthalate, was developed aiming nicotine release. The experiments were conducted with and without the inclusion of a protective layer to prevent volatilization of highly volatile nicotine[64]. The authors identified a slower release and permeation of nicotine transdermal patches in the absence of support, while nicotine transdermal patches with a support layer were released and permeated more rapidly, indicating that the matrix is adequate as a TDDS system.

TDDS provides several advantages such as bioavailability and local drug concentration, which avoid difficulties caused by pH changes in intestinal gastric tract and possible interactions with other drugs. TDDS can replace oral intake in cases of vomiting or diarrhea and, in cases of emergency (unconscious patient), a quick interruption can be done by removing the patch. Although some studies have already been carried out with NR involving this type of application, this subject is still not widespread and demands further investigation.

3.3 Regenerative medicine and tissue engineering

Regeneration of skin, bone, cartilage, and organ tissues has been studied using patient cells cultivated on natural or synthetic substrates, followed by reinsertion, to regenerate damaged or lost body parts, restoring their function, the basis of regenerative medicine and tissue engineering[65]. Such substrates, known as scaffolding, are responsible for providing cellular fixation structure with cell proliferation/colonization, and stable environment, helping tissue remodeling i.e. tissue regeneration. Scaffolding for regenerative medicine and tissue engineering should mimic the functions of the native extracellular matrix[66]. Scaffolds can be produced by conventional molding methods such as casting, electrospinning, 3D printing, or by combining these techniques[67].

Studies involving NRL or NR in scaffolds' processing have been developed to investigate potential applications in the regeneration of skin and bone tissue[3,65,68]. An example of

the application of NRL and NR scaffolds with low cost is the treatment of thermal burns, a serious public health problem causing deaths and considerable psychological trauma.

Biomembranes developed from NRL for bone regeneration have shown promising results[6,22,69]. NRL biomembrane represents an alternative possibility of stimulation and potentiation of osteoconduction and guided bone regeneration, besides being biocompatible, potentially angiogenic, flexible, having mechanical properties, porosity, and permeability[3,6,70]. Additionally, Nascimento et al. showed that calcium/phosphorus compound is surrounded by NR particles due to electrostatic interactions, which can be easily changed in an ionic medium like body fluid, assisting in bone regeneration[71].

It is also worth mentioning the use of dressings commonly used in tissue engineering to improve natural skin healing. Dressings' composition should facilitate epidermal barrier restoration adhered to the lesion, absorbing exudates, preventing infection, dehydration, promoting tissue regeneration, and limiting formation of granulation tissue[43,72]. Several investigations have been carried out regarding the use of NRL as a dressing for skin lesions[4,52,73,74]. Moreover, NRL can be associated with other types of materials, improving their existing properties, or promoting new healing properties.

3.4 In vivo performance

In vivo models aims to characterize the process and evolution of tissue response after implantation of a given biomaterial, that is, to evaluate the tissue-material interface[75]. Few works reported in the literature performed *in vivo* tests using NRL and NR, which include dogs[76], rabbits[6,22,77,78], rats[50,79-83], and humans[73,84,85]. Frade et al. applied an NR biomembrane on alternate days to treat chronic necrotic ulcers on the leg and foot of a 64-year-old patient[86]. The authors observed the effects of granulation stimulation after 15 days of treatment, in addition to pain reduction. After 60 days, granulation tissue reached the edges of the ulcers, so the use of the biomembrane was discontinued, followed by the use of chloramphenicol ointment. After 120 days of treatment, the ulcers were closed before clinical and histopathological reduction. The results were highly satisfactory, providing the patient with greater comfort at dressing changes. Similar data were found by Frade et al. when they evaluated this biomembrane in the treatment of skin ulcers and compared it with a treatment based on fibrinolysin and chloramphenicol. Lesions' healing was induced by intense vascular formation with subsequent re-epithelialization[73].

NR insole was prepared by using a negative alginate personalized mold, which was further applied to diabetic foot treatment to reduce the excessive pressure in the injured regions, significantly reducing the plantar pressures on the patient's feet by attenuating the total maximum force applied to them[84]. The most significant decrease in plantar pressure occurred in the region of ante foot. In the middle region of the foot, the reduction of maximum force was observed. This customized insole was also used in association with a device having a red LED matrix to provide mechanical support and accelerate the healing of diabetic foot ulcers, providing comfort to patients. Patients were satisfied with the results, stating that the system was easy and simple to use contributing to the process of lesions' healing[85].

NRL serum was evaluated as a wound healer by *in vivo* tests in rats undergoing dermabrasion, treated with saline, antiseptic, or latex. The antiseptic solution was compared with a commercial saline solution *in vitro* tests and the effects of cell migration and proliferation were analyzed. The serum of NRL showed viability in concentrations of 1% and 0.1% and migration and proliferation activity with 0.01% of serum[83]. Results showed that the serum did not present toxicity and, compared to other treatments, it was able to stimulate and accelerate the healing of lesions from abrasion.

The effects of applying P-1 (protein extracted from NRL) and Low-level Laser Therapy (LG) to the sciatic nerve of rats after crush injury were evaluated using hyaluronic acid as a carrier agent (1 wt%) with the incorporation of P-1 (0.1 wt%). The animals were anesthetized and the injury site was standardized: the upper and lower ventral spine. A ~2 cm skin incision was made perpendicularly and towards the middle region between the two mentioned points. After this, the muscle fascia was broken over the anterior femoral belly region of the biceps and gluteus maximus, and these muscles were divulsed, not requiring an incision. Finally, the nerve was exposed to the lesion by applying weight with a constant force of 15 kgf for 10 min, which caused the crushing of a circular area of approximately 0.6 cm in diameter. After finishing the lesion, the nerve was replaced and the skin was sutured, followed by medication to prevent possible complications. After 4 weeks, improvements in lesion morphology and morphometry were observed in the LG, P-1 treated, and P-1 + LG groups[87]. The researchers found that this improvement increased with treatment time.

3.5 Commercial performance

Research on NRL began in 1994 in Brazil at the Department of Biochemistry of the University of São Paulo by Professors Dr. Joaquim Coutinho Netto and Dr. Fatima Mrue[13,88]. In 2002, a patent was filed by the University and the company PeleNova Biotecnologia S/A was created, which registered in 2004 the product Biocure®, a biomembrane derived from NRL responsible for inducing the formation of new blood vessels to induce angiogenesis. According to Rosa, its application was recommended for chronic diabetic, vascular, pressure ulcers, post-surgical or traumatic, being applied directly to the surface of the lesion. The first change was recommended 24 h after application[88]. The membrane was discontinued, due to the difficulty of application and maintenance of the product in the patient, and replaced by an ointment called Regederm®, a NR-derived compound in gel-cream form (isolated angiogenic fractions free of compounds that could cause allergy), being registered in Anvisa (Agência Nacional de Vigilância Sanitária) in 2012. During this same period, PeleNova partnered with a Canadian dermatological company, Valeant. In 2017, PeleNova was taken over by the former Brazilian administrators and two years later, the company returns with its market operations, providing bioactive products to licensed companies. The following year, it restructured its operations and became part of Biocure Pharma Biotechnology, a Brazilian group that projects strong

Table 2. Comparison of electrospun fibers' diameter from different biopolymers.

Biopolymer	Solvent	Fiber diameter (μm)	Suggested application	Reference
NR	Tetrahydrofuran; Chloroform; Di-chloromethane; Toluene	~2.0-6.0; ~3.0-6.0; ~2.0-5.0; ~3.0-5.0	Soft tissue engineering	[97]
NRL	Deionized water	N.A	General	[98]
NRL + Poly(vinyl alcohol)		~1.0-4.5		
NR	Toluene	N.A	General	[99]
Polycaprolactone	Chloroform	~1.4		
Polycaprolactone	Di-chloromethane	~1.0	Scaffold	[100]

development in the markets of therapeutics, cosmetics, and actives for various segments[89]. Currently, Regederm® is not being marketed, possibly due to the company's product reformulation after its restructuring.

Another commercially available membrane is Cellprene®, composed of poly(lactic-co-glycolic acid) and polyisoprene, the main component of NR. Cellprene® was developed and patented by the Federal University of Rio Grande do Sul (Brazil) in 2013 for application in tissue engineering[65,90]. According to the literature, Cellprene® has been used in recent studies demonstrating that this biomaterial can act in the maintenance of epithelial cells[65,91,92]

4. Comparison with other Biopolymers

Recently, matrices obtained from electrospun fibers have gained much prominence and have been widely studied as wound dressing and scaffolds in biomedicine due to the ability to modulate cell behavior. Wound dressing and scaffolds are the main devices manufactured from NRL and NR for biomedical applications, thus, a brief discussion is made hereafter to compare the use of different biopolymers in the development of these devices. It is worth noting that, a direct comparison between the studies is difficult due to the different characteristics evaluated in each research.

A high degree of porosity and appropriate pore size are the main characteristics required for wound dressings and scaffolds to provide adequate space for cell propagation and migration, allowing for the proper exchange of nutrients and waste between the scaffold and the environment[93]. Pores smaller than bacteria help prevent infections through the sieve effect and therefore, these devices should have high porosity, preferably at the micro-and nanoscale[94,95]. The porosity and pore sizes of electrospun scaffolds depend mainly on the fiber diameter. Larger fiber diameters provide lower porosity and larger pore size[93,96]. Table 2 lists some data regarding the diameters of electrospun fibers from different biopolymers.

The literature shows that poly(vinyl alcohol) and polycaprolactone electrospun fibers present diameters thinner than ~2 μm, while NR fibers have larger diameters, ranging from ~2 to 6 μm. This fact may hinder the production of NRL and NR devices suitable for biomedical purposes since the polymer chains limit the manufacturing of high-porous biomaterials. Although NRL is inherently hydrophilic, after the drying process, it becomes predominantly hydrophobic[101]. For biomedical applications, a surface with hydrophilic property is needed for adhesion, dissemination, and cell proliferation[102].

NRL fibers can be manufactured by solubilizing in water, but this procedure is little reported in the literature. Most studies involve the production of fibers from NR, which is obtained after drying centrifuged NRL. Thus, another factor that deserves attention is the use of solvents during the production of NR fibers that can cause damage to the cells due to their toxicity. It is also worth mentioning that the studies involving the use of NR in the production of fibers for the development of scaffolds and wound dressing suggest certain applications, i.e., there is still a gap of scientific evidence proving satisfactory results of clinical applications of these devices.

5. Conclusions and Final Remarks

This review described and discussed the advances of NRL and NR biopolymers in biomedical applications and regenerative medicine, highlighting the development of drug delivery systems, scaffolds, wound dressing, and transdermal drug delivery systems. The research on these biomaterials is in full development, referring to applications in skin lesions in the form of dressings, cellular supports, bone regeneration, and release of bioactive molecules, among others. Studies show the high potential of NRL and NR due to the promotion of interesting biological properties and satisfactory biocompatible characteristics. The recent advances in biomedical applications of NRL and NR have demonstrated the multidisciplinarity required for future research that includes the study of the biopolymer (engineering and chemistry), the manufacture of the biomaterial (engineering), and the final application (biology). Current results show that these materials can considerably contribute to medical advancement through the treatment of individuals that requires less time for the cure in an accessible way. The literature lists many suggestions for NRL and NR applications, but *in vivo* tests are still little mentioned, and therefore represent an important gap to be filled. It is necessary to show and prove the real potentiality of these materials, thus, more studies should be developed focusing on the application. With the application of these

materials proven through satisfactory results, the products derived from NRL and NR will present greater chances of being commercialized, exempting the possibility of being discontinued. The simple addition of information on the packaging of the product and scientific communication is indispensable for the popular acceptance of NRL and NR biomedical devices, which present high commercial potential for products focused on tissue engineering and regenerative medicine.

6. Author's Contribution

- Conceptualization – Karina Luzia Andrade; Emanoelle Diz Acosta; Fabrício Faita; Ricardo Antonio Francisco Machado.
- Data curation – Karina Luzia Andrade; Fabrício Luiz Faita; Ricardo Antonio Francisco Machado.
- Formal analysis – Karina Luzia Andrade; Heloisa Ramlow; Juliana Ferreira Floriano; Emanoelle Diz Acosta; Fabrício Luiz Faita; Ricardo Antonio Francisco Machado.
- Investigation – Karia Luzia Andrade. Heloisa Ramlow; Juliana Ferreira Floriano; Emanoelle Diz Acosta.
- Methodology – Karina Luzia Andrade; Heloisa Ramlow; Emanoelle Diz Acosta; Fabrício Luiz Faita; Ricardo Antonio Francisco Machado.
- Project administration –Fabricio Luiz Faita; Ricardo Antonio Francisco Machado.
- Resources – CNPq; CAPES; LINDEN; FAPESP.
- Software –MS Word; MS Excel.
- Supervision – Fabricio Luiz Faita; Ricardo Antonio Francisco Machado.
- Validation – Karina Luzia Andrade; Heloisa Ramlow; Karina Luzia Andrade.
- Visualization – Fabricio Luiz Faita. Ricardo Anotnio Francisco Machado.
- Writing – original draft – Karina Luzia Andrade; Heloisa Ramlow.
- Writing – review & editing – Heloisa Ramlow; Emanoelle Diz Acosto; Fabricio Luiz Faita; Ricardo Antonio Francisco Machado.

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Supplementary Material

Supplementary material accompanies this paper.

Table S1. Biodegradability of NR.

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