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Polylactic Acid: A Bio-Based Polymer as an Emerging Substitute for Plastics

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ABSTRACT

Bio-based polymers attract renewable focus due to natural stocks and the success of limited petroleum resources. Bio-based polymers not only replace polymers with a number of details but also provide new compounds for collections for new details. A list of bio-based polymers presented in this review, focusing on global packaging methods, and marketable performance. Unique processes have been performed to increase the activity and production of similar polymers such as bumps, cellulose, and lactic acid. The quest to produce essential products that can decompose in ever-changing waters such as detergents and cosmetics has continued to add value. Biodegradable polymers are mainly classified as agro polymers and decaying polyester Singh et.al., 2018). Bio-polyester products are obtained mainly through renewable energy. Therefore, consumers are more aggressive with low or non-affiliate ratings of biodegradability paper, leading to head-scratching on the basis of cost-effectiveness and product-friendly products. Additionally, there is no equivalent structure for the removal of biodegradable accoutrements in the end.

Keywords: Biodegradable materials, Bio-based polymers, Renewable resources, Bio-plastic, Natural polymers, Synthetic polymers.

INTRODUCTION

Bio-based polymers are kinds of polymers that are made from normal or organic sources. Part of these polymers are formed directly within the polymeric structure within living organisms (e.g., microorganisms, green growth, active), while the rest are made up of bio-based monomers. Complex bio-based polymers, such as cellulose and energy, are known to have been used for many years. In any case, the utilization of those beginning composites was held directly down to an endless utilize corresponding to bundling, garments, and development. Since about 1990, composite management and biotechnology have allowed the effect of bio-based polymers based on abstract polylactic corrosive (PLC) and polyhydroxyalkanoate (PHA) bright enough to be seen in many refined athletes. Various people commented that these new bio-based polymers have the potential to replace gasoline-based polymers and assist in registering part of the developmental problems posed by the misuse of fuel-based polymers, such as water and soil pollution, the detrimental effect on mortality and fuel dependence. The term life story is anticipated polymers, is the way to two unique sorts of polymers. Decomposing polymers are seen as a material that has physical and synthetic properties that support weakening and degradation when exposed to bacteria, carbon dioxide processes (high impact), methane (anaerobic cycles), and water (strong cycles and anaerobic). Bio-based polymers will decompose (e.g., polylactic corrosion) or indestructible (e.g., bio polyethylene). Bio-based polymers actually hold the nuclear component of the total benefits of global plasticity. At the present day, biopolymers participate in less than 1 of total fertility. At this stage of

development, it is expected that biopolymers will respect less than 1 polymer by 2015 (Doug, 2010). The original bio-composed polymers focus on the thinking of polymers from the cultivation of feed foods such as sorghum, potatoes, and other starch feeds. In any case, the center has moved a long time ago due to the desire to move out of food reserves and major advances in biotechnology. Bio-based polymers, such as conventional polymers, created by bacterial processes of chaos by assembling building blocks (monomers) from endless financial chambers, including lignocellulosic biomass (energy and cellulose), fatty acids, and environmental waste. Common bio-based polymers are another class of bio-based polymers commonly expressed, such as proteins, nucleic acids, and polysaccharides (collagen, chitosan, etc). These bio-based polymers have shown significant improvements since later in terms of event variability and their attractive use.

There are three important ways to create bio-based polymers using sustainable materials:

1. Using standard bio-based polymers with medium differences to meet the bases (e.g., strength).
2. Production of bio-based monomers by age / traditional science followed by polymerization (e.g. polylactic corrosive, polybutylene succinate, and polyethylene).
3. Producing bio-based polymers based on micro-organisms (e.g., polyhydroxyalkanoates).

The various polymers that can be called 'perishable' actually 'rot', 'hydro biodegradable' or 'biodegradable image'. These preparation polymers all fall under a very broad branch of 'polymers that are polluted by the environment. The 'biodegradability' of plastics depends on the fabrication of the fabrication and on the contract of the whole object, not just on the raw materials used for its material. Therefore, Biodegradable plastics may be based on home-grown or counterfeit patches. Ordinary plastic decay is usually based on durable (equal to strength) material and may be unquestionably delivered or assembled from non-combustible material. They're coming beneath polysaccharides (energy, cellulose, lignin, and so forth), proteins (gelatin, fur, silk, and so on), lipid (fat and oil painting), polyesters created with the guide of utilizing studio. Overall result of serious degree client plastics stays administered with the guide of utilizing non-degradable oil grounded polymers. In any case, factors, have made biodegradable polymers financially interesting equal as natural and advantageous enterprises connected with garbage removal and reinforcing expenses of oil based good performing from the consumption of the greatest uninhibitedly convenient stores. Polyesters play a chief capacity as biodegradable plastics due to their surely hydrolysable ester bonds. The polyester circle of family members is the result of large circles, aliphatic (straight) polyester and fragrant polyester (rings). Biodegradable polyester-funded and highly marketed PHA-Polyhydroxyalkanoates, PBS-Polybutylene succinate, PET - Polyethylene terephthalate, PBAT - Polybutylene adipate terephthalate and PTMAT - Polyethylene adipate terephthalate. (John *et al.,* 2006). In this review paper, a high-level perspective on account - rested polymers are produced using the inexhaustible asset and home-grown polymers are brought from assembling and animal starting points is introduced. The outline will secure at the measurement, parcels, activities, and unborn improvements bio-basically based absolutely polymers. Biomass feedstock will be changed over into crude accessories for polymer issues, and furthermore, it is designated "bio-based polymers to act polymer.

Table 1: Classification of bio-based polymers

S.No	Bio-based Polymers	Types of natural polymers
1.	Natural Polymers	(a) Plant source - Polysaccharides: cellulose, starch etc. (b) Animal source - Proteins: gelatin, chitin or chitosan etc.
2.	Synthetic Polymers	(a) Biodegradable - Polylactic acid, and its co- polymers. (b) Non- Biodegradable - Poly methyl methacrylate, Polyester.

Natural bio-based polymers:

Common bio-based monomers are found in nature (industrial centers or animals) and are used exclusively for biomaterials due to their decay, biocompatibility, microstructure, morphology, flexible mechanical sites, and flexibility. Biomaterials appear to be any common or manufactured substance intended to cooperate with conventional clinical co-ordination structures (Williams, 2009). Biomaterials must be environment friendly, borrowable, and harmless, meaning they must be good at fulfilling their role in the proper response of the host (Williams, 1999). In order to meet the basics of the biomedical environment, closely related materials - anything (from possible materials and ceramics to glass and polymers) have been identified. Common bio-based monomers are particularly attractive for biomedical activities as they adhere to models, especially biocompatibility, biodegradability, and high porosity; they can feel another range of combinations and real variants intended to replace the towel and hold common bundles that are attractive in medical practice. Common bio-based monomers and many biopolymers used at specific

high concentrations include collagen, fibrin, fibrinogen, platelet-rich cylinder, alginate, gelatin, egg whites, and -hyaluronic corrosive. A major advantage of bio-platforms from conventional bio-monomers is that they are responsible for enabling cell development (Mazaki *et al.,* 2014). Although conventional polymers such as chitosan, alginate, hyaluronic corrosive, and collagen have been used more and more biologically, the biomedical investigations of biomedical polymer production are relatively new, dating back to the 1960's. In the last fifty years, despite the fact that the victories have been varied, great difficulties actually exist in both the original and translation bases of the standard polymer system. The host response to both the fabric of the handkerchief and the distribution of the drugs depends on the material, body, and common polymer gear packages. To add to the area of chronic problems in the biomaterials system and to revitalize progress, biomaterial researchers inevitably changed their view of emissions, working freely in the limited perception of expulsion from participating oil-based armed forces. By bringing together pizazz experts in science, science, gear, design, and clinical practice,

The release of biomaterials made sense to move everything very quickly. at different times in the past (Ibim *et al.,* 1997). In the design of non-toxic biomaterials, countless important bundles must be considered, created to include proper penetration and analysis of systematic activity (Lloyd *et al.,* 2002). These masses are significantly affected by the component of polymeric biomaterials associated with degradation, a good polymer alone or a polymeric family does not survive. Instead, the standard bio-grounded monomeric activity is accessible to scientists who can be prepared and processed and in addition are truly modified to wash out the details of the biomedical volume of an active substance.

A few applications are introduced by natural Polymers:

Normal polymers are acquired from sticky exudates and plant filaments are being examined and their applications are generally utilized in the drug store and modern fields like thickeners, agar, gelatin and chitosan, and so on. It is likewise utilized in some biomedical purposes like tissue recovery platforms, drug conveyance specialists, and envision specialists. Ordinary polymers are largely used in professional control, providing the same drug transfer as certain polymers used to reduce duplication of dosage and increase the dose limit of the drug in the workplace.

Advantages of Natural Polymers include less toxicity, Biocompatibility, Biodegradable and Easy availability. Whereas, the disadvantages of Natural Polymers cover the serious level of inconstancy in regular material got from creature sources. Fundamentally more mind-boggling and extraction process is exceptionally convoluted and significant expense.

Bio- based polymers and their applications:

Starch:

Starch is a stand-alone polymer in the bio because it occurs in the image as various particles. The absolute true power of photosynthesis in manufactory — a carbon -based polymer that is most likely made from grain from altered sources containing wheat, rice, corn, and potatoes. In fact, starch contains essential polysaccharide amylose and a large proportion of the expanded polysaccharide amylopectin. In various places, thermoplastic starch is in a growing state within attention. Warm and mechanical power strips can dramatically separate and open up resources to compare how much plasticizer is available. Tg varies between - 50 ° C and 110 ° C, and modulus is associated with polyolefins (Jane, 1995). The atomic composition of a starch atom is complex, and to some extent indirect, intricate. Endless starch thermoplastics are heard from the back-to-back warning feature - a feature of glossy expansion second, showing broadened harshness. Plasticizers take to the live industrial facility to convey starch plastics with compulsory areas tantamount to polyolefin-chose bundling. Plasticized starch blends and combinations and additionally synthetic contrasts might get these merchandises, decaying polymers have sufficient mechanical strength, ease of use, and lots of water separators to combine attractive materials and purchases. (Maurizio *et al.,* 2005). The purposes of thermoplastic starch polymers include screen, equal with respect to shopping, vittles, and fishing trap sacks, overwraps, flushable clean thing, stopping stuff, and oddball mulch pictures conceivable tomorrow uses could include head free stacked bundling and infusion separated impacts comparable as 'hold-away' throw holders. Starch and beans are larger than the wide range of activities both in the food and non-food areas.

Cellulose

Cellulose is a very common element in cell dividers, everything is equal. Cellulose is a complex polysaccharide with translucent morphology. Cellulose compares to starch where glucose units are linked to β chains, while starch bonds are a major part of the connection. The most important source of raw material for the effect of cellulosic plastic fibers is cotton and wood. Plant resistance disappears from antacid and double disulfide to form gooey, which is also converted into cellophane in the form of cellophane, followed by a shower of sulfuric corrosive and sodium sulfate. There are any techniques used to separate cellulose into different parts of wood (Yan *et al.,*

2009). The basic cellulose decisions in targeted products are the production of cellulose acetic acid, cellulose esters (cutting, expulsion, and flicks), and renewable cellulose fiber. Cellulose is a strong polymer and has a high elasticity of 62 to 500 MPa. increase of 4 (Bisanda and Ansell, 1992; Eichhorn *et al.,* 2001). Consequently, in order to get around the basic cellulose handling issues, it is necessary to be uniform, plastic, and mixed with various polymers. Compulsory and warm lots vary from one combination to another, unlocking the number. By design, direct cellulose can be transferred using a specific pattern of very small organisms. Bacterial cellulose is characterized by its innocence and high potency. Having a powerful nature can be used. To date, bacterial cellulose activity other than diet and biomedical activities appear prematurely due to its high charge. A variety of activities include sound abdomen, mining, beauty care products, material gas recovery, and bonds.

Chitin and chitosan

Chitin and chitosan are many common amino polysaccharides and bio-based polymers found in prawn and crab shells. Currently, chitin and chitosan are commercially imported through a process of extraction from crabs, shrimps, and prawn squanders (Roberts, 1997). The extraction of chitin is a potent cycle in terms of degradation of minerals by corrosion and salt degradation followed by deacetylated in chitosan (Roberts, 1997). Chitin can also be delivered using combined hydrolysis or aging interactions, however, these cycles are not financially achievable at the current rate (Win and Stevens, 2001). Currently, there are not many modern chitin-scale plants and whole chitosan found in the USA, Canada, Scandinavia, and Asia. Chitosan exhibits interesting properties including biological decay, biological compatibility, material density, high mechanical strength, good filming features, and low cost (Marguerite, 2006; Virginia *et al.,* 2011). Chitosan is used in a variety of materials and applications ranging from drugs and remedies to water purification and plant protection. In all applications, various chitosan structures are required, which change with the level of acetylation and atomic weight. Due to its low anti-inflammatory, biocompatibility, and bioactivity performance, chitosan has become a distinctive feature in various programs such as biomaterials in clinical gadgets and as drug modifications (Bae and Moo-Moo, 2010; Ramya *et al.,* 2012). Chitosan is used in shampoos, flushes, and long-lasting hair conditioners. Chitosan and its subsidiaries alike operate in a healthy leather industry. Chitosan can act as a skin lotion, and due to its low cost, can counteract the hyaluronic corrosive in this application (Bansal *et al.,* 2011; Valerie and Vinod, 1998).

Collagen and gelatin

Collagen is a large soluble sinewy protein that is soluble in the grid outside cells and in connective tissue. In fact, it is the most abundant protein in animal collections. The most common sources of collagen are pig skin, cow stow, and pig bones and bones. However, modern collagen use is found in non-mammal species (Gomez-Guille *et al.,* 2011). Gelatin is obtained by hydrolysis of collagen. The rate of collagen conversion into gelatin depends on pre-treatment, temperature, pH, and release time (Johnston-Banks, 1990). Collagen is one of the most important organisms due to its biocompatibility, biodegradability, and weak antigenicity (Maeda *et al.,* 1999). The primary use of collagen films in ophthalmology is similar to the therapeutic frameworks for the slow arrival of synthetic drugs (Rubin *et al.,*1973). It was also used for tissue design which includes skin replacement, bone replacement, and artificial veins and valves (Lee *et al.,* 2001). The traditional, visual, preparation, and drug use of gelatin is highly dependent on its gel-forming properties. Since the end of the food business, a growing number of new gelatin applications have been found in the material in line with the growing pattern to be adopted by more general engineers (Gomez-Guille *et al.,* 2011). These include emulsifiers, foam specialists, colloid solvents, non-corrosive film-forming materials, and microencapsulating specialists.

Synthetic bio-based Polymers:

Synthetic polymers are the most frequently produced polymers. Polymers are those that comprise the lower backed units called monomers. Polyethylene appears to be one of the purest polymers; contains ethane or ethylene as a monomer unit, while the straight polymer is known as high-consistency polyethylene-HDPE. Various polymeric accessories have chain-like structures that run like polyethylene. Formed polymers are rarely presented as “plastic”, where the bones found in the source are nylon and polyethylene. Polymers, which are reinforced with monomer bonding units, without material recycling, are called polymers augmentation or similarly called chain development polymers. All of these are extracted to make polymers that are produced. The few engineering polymers we use in our general life include the nylon used in building materials and manufacturing process. Teflon benefited from a non-abrasive refinement, polyvinyl chloride was used for the pipes. The PET presses we use are composed polymers called polyethylene terephthalate. Plastic covers and utensils contain polymers made of polythene, and car tires were created from Buna rubber. Regardless of the possibility, on the other hand, environmental impacts have arisen, the use of these bio-produced polymers - plastics

and oil-based ones as they should not rot. They can be reused in light tricks to create thin strands or intricate passages (High Extension), smoothness of the system and the integration of refined structures.

A few applications are introduced by Synthetic Polymers:

A polymer called Polyethylene is used in plastic bags and film wraps. Polyethylene is used in bottles, electrical purchases, toys, and so on. Polyvinyl Chloride (PVC) is used for sides, pipes, and flooring purposes. Formulated polymer Polystyrene is used in storage and assembly rooms. Polyvinyl acetic acid derivation is used in plastic bonds and maquillages.

Advantages of Synthetic Polymers:

In nature, manufactured polymers are incredibly widespread. They are set in a variety of pictures. The significant polymer in superglue is methyl -2-cyanopropenoate, which is a commodity we use on a diurnal basis. At the point when RTV silicone is got dried out, it solidifies and is applied to create gaskets for motorcars. Polyester is a material taken from the fabric area, through which we concede a lot of our more distant family impacts, and nylon is utilized in socks and ropes. Engineered polymers have a great deal of delicious bundles, which is a major expansion. They've sensible energy, rigidity, resistivity, synthetic inaction, and various packages.

Disadvantages of Synthetic Polymers:

Substance inactivity, or resistance to various qualities of compound laugh uncontrollably, is a positive lot in various manufactured polymers. This equivalent quality comparatively implies they endure a long second in the wake of being disposed of, which is very wicked to the landscape and ought to be stayed away from. Be that as it may, they can get a huge number of issues. On the off chance that these significant polymers aren't properly stored. These are varieties of synthetic polymers. There are various synthetic polymers developed so far. Let us study in brief about numerous of the synthetic polymers operated in run-of-the- factory life. Synthetic polymers after degradation causes harm on aquatic biota.

Nylon

Nylon has a place and family of polymers that are made and known as polyamides. Followed on February 28 during 1935, Wallace Carothers was assigned to register for the DuPont examination. It is an extensively worked polymer. Nylon gets retained in hydrogen connecting with, dislike the decontaminated hydrocarbon polymers which fabricate the majority of the plastics.

Polyvinyl Chloride:

Polyvinyl Chloride, or PVC, is the third-most regularly utilized plastic propelling polypropylene and polyethylene. This PVC is applied to structure objects as it's known to be more grounded and sensible than particular druthers like iron. PVC is utilized in attire, electrical string sequestration containing various different applications, subbing elastic.

Low-Consistency Polyethylene:

The Low-Consistency Polyethylene polymers are the most standard sort of manufactured polymers, which are widely utilized in homes. LDPE is a portrayal of thermoplastic which is ready from the monomer called ethylene (Manzoor et.al., 2021 **B)**.

Polypropylene:

Polypropylene likewise called polypropene, is a portrayal of thermoplastic manufactured polymer which is taken advantage of assortment of tasks like bundling, naming, writing material, textures, plastics, and in appropriate holders, lab accessories and so on. A few distinct embodiments contain Thermoplastic Polyurethane, Teflon, Polystyrene, High Thickness Polyethylene, Neoprene, and so forth.

Polylactic Acid :

Polylactic acid (PLA) has been perceived because of the way that 1845, yet at this point presently not promoted till mid-1990. PLA has a collection of members of the aliphatic polyester family with the first lactic corrosive unit. The monomer lactic corrosive is a hydroxyl carboxylic corrosive, which can be obtained by disinfection from slop (escape) or sugar obtained by stable cash filters. Slime has the advantage of outfitting an excellent feedstock for unrest which winds up in an inordinate - virtue lactic corrosive, which is needed for a strong fake cycle. L-lactic corrosive or D-lactic corrosive is achieved depending on the microbial pressure applied to all uncontrolled processes. PLA might be integrated from lactic corrosive through method of method for direct poly buildup response or ring-laying out polymerization of lactide monomer. In any case, it is delicate to help unreasonable sub-atomic weight PLA through poly buildup response because of water compliance all through the response (Erwin *et al.,* 2007). It has extreme explicit attributes, along with exact clarity, radiant appearance, exorbitant seriousness, and usefulness to endure vivid types of handling conditions. PLA has changing over into accomplice recognition including explicit for a broad cluster of items and is available for logo skipping new bundling activity. Microplastics rectangular degree normally identified in the nature, the destructive 1/2 of is referred to and for the greatest component obscure. One vital assignment in assessing the unsafe and basic

legitimate liability of microplastics to individuals and furthermore the environment connected with substantial and compound bundles, adaptation and activity of the patches. (Bergmann *et al*., 2015). Microplastics in the biological system rectangular measures the building up to outfitting and normalized approaches truly do now never again make due. All the presence of microplastics of every one of the sizes in the face, and waste water have exchange of the upheld microplastics (Manzoor et. al., 2020 & 2021 A). Polylactic has been coordinated to modernize the indistinguishable classic petrol overall grounded totally thermoplastics, because of the incredible admixture of areas it has. It's one of everything about greatest promising biopolymers utilized as of now and fuses an impressive degree of utilizations like medical services and logical exchange, bundling, car applications and so forth. As when contrasted with perfect biopolymers, PLA notorious serious benefits equivalent eco-accommodating. It is, inexhaustible, short-lived, reclaimable and compostable biocompatible. It 'nontoxic.

Applications:

Currently PLA is commonly used in food mixing. A few items manufactured using PLA include guards, flatware, cups, and silver plates. Drive after PLA approval to consolidate its biological decay. A very large number of PLA types produce an attractive look. That's important to others, integration works. Similarly, unbearable due to its decay and repaired equipment parcels, PLA is tracking down promising work in horticulture. Its clarity makes it ideal for the construction of coated paper or disposable insecticide-spraying equipment and sewage.

Used as a cover film, toward the end of the season, PLA-ground mulch cover can be left in the field, where it gradually deteriorates into smaller pieces that may be harvested which means that without problems PLA is reused. On clinical obligations such as implants, stents, and bone support chips, the PLA mechanical packages can be modified to suit their compass counterparts, making reconciliation smoother.

The use of PLA as an embedded substance is protected, as the degradation of PLA by hydrolysis causes lactic corrosive corrosion, a factor that is killed by normal body digestion. There were also a few applications that included PLA in 3D printing. Nature Works has disrupted a joint venture with 3DOM to encourage a few. Stylized polylactic markings for 3D printing and Export methods for 2015 (Dorozhkin, 2009; Garlotta, 2001).

Table 2: Uses of PLA and their compounds in some actions

Polymers	Uses	References
PLA/chitosan PLA/PLGA/ chitosan PLA	Drug transit/ medicine discharge.	(Jeevitha and Kanchana, 2013; Jayanth and Vinod 2012)
PLA/HA Composites	pervious scaffolds for cellular operations.	(Jung-Ju *et al.,* 2012)
PLGA-CaP	Bone obsession bone, scales, legs, and orthopedic uses.	(Huan *et al.,* 2012)
PDLLA	Clothes lined with immature items.	(Schmidmaier *et al.,* 2001)
PLA and PLA Blends	Packaging moving pictures, electrical widgets, bottom mats, automotive extra region	(Rafael *et al.,* 2010) (Incomplete)
PLA	Clothes usages	(Gupta *et al.,* 2007; Avinc and Akbar, 2009)
PLGA/PGA	Ovine pulmonary gate replacement	(Williams *et al.,* 1999;; Cheng *et al.,* 2009)

Production of PLA

PLA (polylactic corrosive) is usually produced using sugar from maize, cassava or sugarcane starch. To turn the corn into plastic, slices of corn are soaked in sulfur dioxide in boiling water, where their components split into starch, proteins, and fibers. The slices are then ground and cornstarch separated from the starch. Starch contains long chains of carbon particles, like carbon chains in plastic from non-renewable energy sources. A few orange extracts are combined to form a long-chain polymer (a large particle that covers the regeneration of modest units) which is a block of plastic structure. PLA can look and act like polyethylene (used in plastic films, presses and containers), polystyrene (Styrofoam and plastic cutlery) or polypropylene (bulk, car parts, building materials). Minnesota Nature Works is probably the largest organization to bring PLA under the brand name Ingeo.

Table 3: Bioplastic production

S.No.	Materials	References
1.	**Maize, wheat**: corn kernels are processed and processed, dextrose is extracted from the starch.	Elizabeth 2006
2.	**Sugarcane**: Sugarcane creation and transport to sugar factory, sugarcane change into crude sugar, maturation of crude sugar from sugarcane to deliver lactic corrosive, transformation of lactic corrosive into lactide and PLA by Absolute Corbion PLA.	Marao et.al. 2019

3.	**Cassava**: Cassava contains a lot of starch, which can be used in the construction of bioplastics. This opportunity is an amazing opportunity to develop cassava as a natural alternative to eco-accommodating plastics. In fact, cassava has great potential for the creation of bioplastics from Indonesia. is the third largest cassava maker in the world.	Firdaus et.al.,2011

CONCLUSION:

Bio-based polymers are gaining increasing attention due to environmental concerns and the perception that the world's petroleum resources are limited. Bio-based polymers not only replace existing polymers in a variety of applications but also offer a combination of new properties for new applications. Today, with advances in biotechnology and public awareness, biobased polymers can be found in many applications, from consumer goods to high-tech applications. However, despite these advances, there are still some drawbacks that hinder the wider commercialization of biobased polymers in many applications. This is primarily due to performance and price compared to traditional counterparts, which, remain a major challenge for biobased polymers.

Declaration: *We also declare that all ethical guidelines have been followed during this work and there is no conflict of interest among authors.*

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