Nanocellulose as a new sustainable material for various applications: a review

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ABSTRACT

Purpose: This paper presents a comprehensive review of nanocellulose and its application in several applications, including composites, biomedical, and food packaging fields.

Design/methodology/approach: General explanations about cellulose and nanocellulose have been described. Different types of nanocellulose (cellulose nanofibers, cellulose nanocrystals, bacterial nanocellulose) as well as their isolation processes (mechanical process, chemical process) have been reviewed. Several surface modifications have been explained to improve the dispersion of nanocellulose in non-polar polymers. The possible utilization of nanocellulose in composites, biomedical, and food packaging fields have also been analysed.

Findings: This review presents three application fields at once, namely composites, biomedical, and food packaging fields. In the composite field, nanocellulose can be used as a reinforcing agent which increases the mechanical properties such as tensile strength and toughness, and thermal stability of the final composites. In the biomedical field, nanocellulose is reinforced into hydrogel or composites which will be produced as tissue scaffolding, wound dressing, etc. It is found that the addition of nanocellulose can extend and control the drug release. While in the packaging field, nanocellulose is added into a biopolymer to improve the barrier properties and decrease the water and oxygen vapor transmission rates.

Research limitations/implications: Nanocellulose has a hydrophilic nature, thus making it agglomerated and difficult to disperse in most non-polar polymers. Therefore, certain surface modification of nanocellulose are required prior to the preparation of composites or hydrogels.
Practical implications: Further research regarding the toxicity of nanocellulose needs to be investigated, especially when applying it in the biomedical and food packaging fields.

Originality/value: This review presents three application fields at once, namely composites, biomedical, and food packaging fields.

Keywords: Nanocellulose, Nanocomposites, Nanofiller, Reinforcing agent, Surface modification

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1. Introduction

Public concern for the environment is increasing through efforts to reduce the consumption of fossil-based materials and switch to the use of environmentally friendly and renewable materials. In recent years, research on the use of green, renewable, and sustainable materials to produce environmentally friendly products with high value-added properties has attracted many researchers [1]. Lignocellulosic biomass is considered as the source of natural fibers which can substitute the use of non-renewable petroleum-based polymers. The cell wall of lignocellulosic biomass is mainly comprised of lignin, hemicellulose, and cellulose [2]. Among those three components, cellulose is one of the materials that received the most attention from the researchers.

Cellulose is known as the most abundant biopolymer on Earth [3]. It is the main component of lignocellulosic materials which are comprised of around 35-50% of the plant cell wall. Due to its rich hydroxyl groups and strong hydrogen bonding, cellulose shows excellent mechanical and thermal properties [2,4]. In addition, cellulose is regarded as biodegradable, which makes it a good alternative for the production of cellulose-based composites [5].

With the advance of nanotechnology, the production of nanoscale cellulose fibers, known as nanocellulose, has attracted many researchers [6]. Nanocellulose is a material which is isolated from cellulose where at least one of its dimensions is in nanoscale (<100 nm) [5]. Generally, there are three types of nanocellulose, including cellulose nanofibers, cellulose nanocrystals, and bacterial nanocellulose. Due to the reduction of its size, nanocellulose has a higher surface area, crystallinity, better optical transparency, and improved mechanical, thermal, and barrier properties. Additionally, nanocellulose is renewable, biodegradable, biocompatible, and nontoxic [7,8]. These beneficial properties made nanocellulose a promising resource for reinforcement in polymer nanocomposites [5].

It was reported that the use of nanocellulose as reinforcement in composites can produce nanocomposite materials that are lightweight, transparent, with high mechanical and thermal properties [4,9,10]. These nanocellulose-based materials could be further applied in various fields, including packaging, construction, furniture, biomedical fields, etc. [11]. At present, many studies have reported that the synergistic effect of nanocellulose produces a strengthening effect of more complex polymer composites. However, the strengthening interaction mechanism between polymers has not been fully explained in detail. In this regard, it is very important to understand the structure and physicochemical properties of nanocellulose, especially in terms of modifying its functional properties to develop its potential applications.

However, the main disadvantage of using nanocellulose is its hydrophilic nature, which makes it difficult to disperse in most non-polar polymers. Hence, to improve the ability of nanocellulose to be dispersed in non-polar polymers and broaden its application, the surface of nanocellulose needs to be modified, such as by the acetylation process [6,12], and cationization process [13-15]. The method of modifying the functional properties of nanocellulose involves a complex interaction mechanism between polymer functional groups. Each method has advantages and disadvantages. In general, the modification method needs to consider the purpose of the modification and the factors of the process conditions and is environmentally friendly. The modification process causes changes in particle morphology, surface microstructure, crystal structure, physical and chemical properties of nanocellulose. Changes in these characteristics need to be known because they will affect the final performance of nanocellulose.

The increasing attention and interest of researchers to explore the potential of nanocellulose as a sophisticated multifunctional material towards the development of new applications. Thus, this article can serve as an extensive review that summarizes the literature and recent advances...
regarding the potential applications of nanocellulose in several fields. In this review article, we are discussing the potential application of nanocellulose in several fields. Firstly, general explanations about the structure of cellulose and nanocellulose, as well as the isolation process, are described. Then, several surface modifications of nanocellulose to improve their compatibility with non-polar polymers are explained. Lastly, the potential application of nanocellulose in composites, biomedical, and food packaging fields are reviewed.

2. Cellulose and nanocellulose

Cellulose is a renewable and biodegradable biopolymer consisting of linear homopolysaccharide of anhydro-\(\alpha\)-glucose units linked together by \(\beta\)-1,4-linkage with cellobiose repeating unit (Fig. 1). The anhydroglucose unit, known as the monomer of cellobiose, consists of three hydroxyl groups that form strong inter- and intra-molecular hydrogen bonds. The intramolecular hydrogen bond is formed between the \(C_3\) hydroxyl group on the glucose unit, and the \(O\) pyranose ring atom present in the nearest glucose unit, the hydroxyl group at \(C_2\) and the \(O\) at \(C_6\) of its neighboring glucose unit. An intermolecular hydrogen bond is formed between the \(C_6\) hydroxyl groups and the \(O\) at \(C_3\) [16]. These hydrogen bonds play a major role to the packing of the crystalline parts and physical properties of cellulose, such as toughness, strength, hydrophilicity, fibrous, insolubility in most aqueous solvents, and high resistance to most organic solvents [2]. The crystalline structure of cellulose, known as elementary fibrils, is formed by cellobiose units that are linked together. The fibrils are then bundled together to form micro-fibrils, then formed macro-fibrils known as cellullosic fibers [1]. These cellullosic fibers usually have a diameter of around 10-50\(\mu\)m and a degree of polymerization (DP) which ranges from 1500 to 3500, depending on its nature and the isolation process. The characteristics of cellulose are mainly affected by its DP and polymeric chain length [17].

Fig. 1. Cellobiose repeating unit [2]

Cellulose can be extracted from various sources, such as plants, woods, bacteria, marine animals e.g. tunicates, etc. In plants, cellulose acts as the major part of their cell wall as well as their supportive backbone. Cellulose in bacteria is mainly produced from many species of nitrogen fixing bacteria to access oxygen and defend themselves against chemical and ultraviolet effects [18]. Cellulose consists of both ordered and less ordered regions, known as crystalline and amorphous regions, respectively. The crystalline region has higher density and is more resistant to chemical, mechanical, and enzymatic treatments compared to the amorphous region. The crystallinity of native cellulose varies from 40–70%, depends on the nature of cellulose and its isolation process [1,17].

Based on its inter- and intra-molecular orientations, cellulose can be classified into four different types of polymorphs (Fig. 2); cellulose I, II, III, and IV [1]. Cellulose I, known as native cellulose, is found in nature and classified into cellulose I\(_\alpha\) (usually isolated from bacteria) and I\(_\beta\) (usually isolated from plants) [19]. Cellulose II, known as mercerized and regenerated cellulose, is obtained from the treatment of cellulose I using aqueous sodium hydroxide.

Fig. 2. Four different types of cellulose polymorphs [20]
The main difference between cellulose I and II is that the atom layout of cellulose I is in a parallel direction, whereas cellulose II is in an anti-parallel direction. Cellulose III, consist of cellulose III$_1$ and III$_2$, is obtained from the treatment of cellulose I and II using liquid ammonia or with certain organic amines, such as ethylene diamine (EDA), followed by washing with alcohol, respectively. Cellulose IV is obtained from the modification of cellulose III, which is processed at high temperature in glycerol [17].

Nanocellulose is a new class of fiber which is extracted from cellulose. Compared to cellulose, nanocellulose has a higher surface area due to the reduction of its size. Typically, nanocellulose has a diameter less than 100 nm and length of several micrometers. Due to this size reduction, nanocellulose has better properties, such as better transparency, lower density (around 1.6 g/cm$^3$), lightweight, as well as better mechanical and thermal properties [2,7]. Nano-cellulose was found to have high a stiffness up to 220 GPa and a tensile strength up to 10 GPa [7].

### 3. Nanocellulose isolation

Typically, the isolation of nanocellulose is comprised of two main stages: pretreatment methods to obtain pure cellulose and transformation from cellulose into nanocellulose. During the pretreatment process, hemicellulose, lignin, and some extractives, including resin, wax, flavonoid, fatty acids, tannin, etc. are partially or completely removed from the lignocellulosic materials [1]. The pretreatment process can effectively cut cellulose, break the hydrogen bonds, give new properties to cellulose and improve the nanofibrillation process. However, the results of each pretreatment process are different according to the type and characteristics of the fiber used [21]. The pretreatment method can improve the nanofibrillation process and reduce its energy consumption, thus increasing nanofibers production [17].

There are two common methods that are usually conducted for the pretreatment process, including acid-chlorite and alkaline pretreatments. Acid-chlorite is commonly known as delignification or bleaching process [22,23]. In this process, lignin and other components are removed by using the mixture of distilled water, sodium chlorite, and acetic acid. Meanwhile, in the alkaline process, the amorphous region of hemicellulose and the remaining lignin content are removed by using an alkali, such as 4-20 wt% of sodium hydroxide [22,24].

Commonly, the transformation from cellulose into nanocellulose can be conducted in several methods, including mechanical, chemical, enzymatic, and combinations of two or more methods [25]. Different transformation methods will lead to different types and properties of produced nanocellulose [2]. Generally, nanocellulose is categorized as cellulose nanocrystal (CNC), cellulose nanofibers (CNF), and bacterial nanocellulose (BNC). Both CNC and CNF are isolated from plant-based materials, while BNC is isolated from bacteria. Cellulose nanocrystal, usually also known as cellulose nanowhisker, is isolated from plant-based materials through chemical treatments, such as acid hydrolysis. It consists of short-rod-like shape fibrils with diameter ranges from 2-20 nm and length from 100-500 nm. CNC has a higher crystallinity of around 54-88%. The high crystallinity value results due to the acid hydrolysis process [20,26]. During acid hydrolysis, the amorphous parts of cellulose are hydrolyzed and removed, while the crystalline parts are still maintained. Thus, its crystallinity becomes higher [4]. The morphology of cellulose nanowhiskers obtained from different sources is presented in Figure 3.

The two most common acids used to produce CNC are sulfuric and hydrochloric acid. Both of them produce CNC with different characteristic. By using hydrochloric acid, the produced CNC is difficult to disperse in an aqueous medium and tends to flocculate [30]. Meanwhile, by using sulfuric
acid, the CNC can be easily dispersed in an aqueous medium as a stable colloid system. This might happen because of the esterification process that occurs on the surface hydroxyl group of cellulose due to charged sulfate esters [31-34]. There are several factors that affect the properties of nanocellulose produced by acid hydrolysis, such as acid concentration, reaction time, and temperature used during the process. Even though acid hydrolysis can produce nanocellulose with high crystallinity, it has a limitation in terms of the acid wastewater generated from the process [2]. Recent technological developments have resulted in a few sustainable and environment-friendly methods.

Cellulose nanofibers are isolated from plant-based materials through mechanical treatments which use a high shear force to breakdown the cellulose fibers into nanofibrillated cellulose in the longitudinal axis [2,4]. Common methods that are used include grinding [35], ultrasonication [36], combination of ultrafine grinding and ultrasonication [37], high pressure homogenization [38], high shear refining, cryocrushing [39], microfluidization [40], ball milling [29], etc. CNF consists of elongated and flexible fibrils with diameter ranges from 1-100 nm and length ranges from 500-2000 nm [10,41]. Due to its longer length compared to CNC, CNF has a higher aspect ratio (ratio of length to diameter). The limitation of using mechanical treatment to produce nanocellulose is that it needs very high energy, thus it usually combines with other methods to decrease the energy used [42]. The morphology of cellulose nanofibers is presented in Figure 4.

Another method used to isolate nanocellulose is by enzymatic hydrolysis. This method allows the process to be performed in milder conditions, however longer hydrolysis time and higher cost for enzymes are needed. Thus it usually combines with other methods [5,46]. By using enzymatic hydrolysis, no chemicals and solvents are needed, thus it is more environmentally friendly compared to other methods [47]. Also, enzymes work more specifically and selectively, yielding higher and almost pure nanocellulose, has high saccharification efficiency, can penetrate easily, and lower energy consumption is needed [47-49]. There are several factors that affect the enzymatic hydrolysis process, such as enzyme concentration, the duration of enzyme activity, temperature needed during hydrolysis, and available surface area of cellulose [50].

The enzymes that are responsible for transforming cellulose into monosaccharide are cellulases enzymes,
including endoglucanases, exoglucanases, and cellobio-hydrolases. Firstly, endoglucanases access the amorphous parts of cellulose and the internal bonds of the glycan chains are randomly separated, thus producing non-reducing ends of cellobio-oligosaccharides. Then, these non-reducing ends are hydrolyzed by cellobiohydrolases to produce cellobiose. Subsequently, the cellobiose is hydrolyzed by β-glucosidase to produce glucose. The glucose produced is then released from the non-reducing ends of the soluble cellobio-oligosaccharides [5]. The morphology of nanocellulose produced by enzymatic hydrolysis is presented in Figure 6.

4. Surface modification of nanocellulose

Recently, the use of nanocellulose as a reinforcing agent has gained much interest by researchers. Basically, nanocellulose can disperse well in a polar polymer, due to its hydrophilic nature. This nature is attributed to the presence of three hydroxyl groups that are attached to each glucopyranose ring. Besides, due to their large surface area and strong hydrogen bonds, some aggregates are formed and result in inefficient compounding with most of hydrophobic polymers [53].

To broaden the application of nanocellulose with non-polar polymers, their surface needs to be modified by using physical, chemical, and biological approaches [49]. According to a previous article review by Islam et al. [54], several physical approaches that can be conducted are electric discharge (plasma treatment), ultrasonic treatment, irradiation, and surface fibrillation. However, chemical approaches, including esterification, cationization, carboxylation, silylation and polymer grafting are the most applied surface modification methods among others [32]. During the process, certain chemical groups are incorporated into the surface of nanocellulose to substitute its hydroxyl groups. This process aims to improve nanocellulose compatibility as well as dispersion by increasing the amount of stable positive or negative charges on its surface [55]. Chemical modification needs to be done in such a way that it only changes the surface of nanocellulose, thus maintains its original morphology and the integrity of its crystal [54].

Among other chemical modification processes, acetylation and carboxy-methylation are mostly conducted [32]. The acetylation process is quite simple, effective, and less toxic compared to other processes [6,12]. During acetylation, acetyl groups, such as acetic anhydrate are introduced into the surface of nanocellulose. During the acetylation process, an excess of acetic anhydrate and inert atmospheric conditions are used as the acetylation process is equilibrium limited. Firstly, the acetylation process occurs on the most accessible hydroxyl groups found on the surface or disordered (amorphous) region of nanocellulose. Then, the process goes further on the less accessible hydroxyl groups which are usually found inside the cellulose crystals [6]. Meanwhile, in the carboxy-methylation process, carboxymethyl groups are introduced onto the surface of nanocellulose. One of the drawbacks in using chemical approaches is that the process makes nanocellulose become less natural, thus making it less likely to be accepted in biomedical fields [32].

Several studies have reported that chemical surface modification involves nanocrystalline cellulose and covalent bonds [56]. These modifications are grouped into three categories as shown in Figure 7, namely (1) hydroxyl groups substitution with small molecules (as indicated with red arrows in Fig. 7), (2) polymer grafting based on the “grafting onto” strategy with different coupling agents (as indicated with blue arrows in Fig. 7), and (3) polymer grafting based on the “grafting from” approach with a radical polymerization involving ring opening polymerization (ROP), atom transfer radical polymerization (ATRP) and single-electron transfer living radical polymerization (SET-LP) (as indicated with yellow arrows in Fig. 7) [57].
Fig. 7. Surface covalent chemical modifications of cellulose nanocrystals (CN). PEG: poly(ethylene glycol); PEO: poly(ethylene oxide); PLA: poly(lactic acid); PAA: poly(acrylic acid); PNiPAAm: poly(N-isopropylacrylamide); PDMAEMA: poly(N,N-dimethylaminoethyl methacrylate) [56,57]

In addition, surface chemical modification can also be carried out through non-covalent bonds, namely by physical interaction or adsorption of molecules or macromolecules. The nanocellulose surface can be modified using surfactants as stabilizing agents. Surfactants have two main groups, namely hydrophobic and hydrophilic groups. The hydrophilic groups of the surfactant molecule may bond on the surface of nanocellulose whereas the hydrophobic groups may extend out providing a non-polar surface and lowering the surface tension of the nanocellulose. Several researchers have modified the surface of nanocelluloses with surfactants such as a cationic surfactant cetyltrimethylammonium bromide-CTAB [13], an anionic surfactant consisting of acid phosphate ester of ethoxylated nonylphenol [58], and macromolecules of xyloglucan oligosaccharide-based triblock copolymer [59].

In addition to physical and chemical approaches, enzymes can also be employed to modify the nanocellulose surface. According to Gulitz and Paulo [60], several enzymes that are usually used for modifications include the class of hydrolase, such as glycosidases, proteases, and lipases, as well as the class of oxidoreductases, such as tyrosinase, laccase and peroxidase. The modification process using enzymes is safer and more advantageous, because it works more specifically compared to chemical approaches. In addition, the reaction takes place in milder conditions and there are no destructive transformations occurring on the surface of polymer [48,49].

5. Nanocellulose as reinforcement in composites

The reinforcing effect of nanocellulose is one of the most interesting topics in polymer nanocomposite fields. Polymer nanocomposites are defined as the materials that consist of polymers as the matrix/continuous phase and nanomaterial as the filler/reinforcing phase [11]. Many researchers reported that with the incorporation of nanocellulose, even at very low concentration into the polymeric matrix, the mechanical, thermal, and barrier properties of the final nanocomposites could be improved.

The improvement of mechanical properties of nanocomposites happened due to the the presence of strong inter- and intra-molecular hydrogen bonds with the polymer matrix. Also, the high aspect ratio of nanocellulose could also contribute to the entanglements in the nanocomposite, thus improving its mechanical properties [61]. The tensile strength and Young’s modulus of nanocomposites can be increased up to a certain value by the addition of nanocellulose. However, further addition of nanocellulose
can cause agglomeration that will decrease the mechanical properties of nanocomposites [11].

In addition, the formation of strong hydrogen bonds between nanocellulose and the polymer matrix can improve the thermal properties of nanocomposite. The addition of nanocellulose could also increase the barrier properties of the nanocomposite. When nanocellulose is dispersed well in the polymer matrix, strong interfacial interaction between the nanocellulose and polymer matrix is formed, thus reducing the chain segmental mobility and decreasing the penetrant diffusivity [62].

Based on the production process, the processing of polymer nanocomposites can be divided into physical methods (solution processing, melt mixing, electrospinning) and chemical methods (in-situ polymerization). In solution processing, nanocellulose is dispersed in the base polymer or pre-polymer solution. Then, the mixture of nanocellulose and polymer is agitated to obtain a homogeneous mixture. After that, the solution is casted and the solvent is evaporated to obtain a solid polymer nanocomposite [63]. When a polar polymer is used as the matrix, the uniform dispersion of nanocellulose in the matrix can be achieved due to the same hydrophilic nature of both materials. However, when a non-polar polymer is used as the matrix, the surface of nanocellulose needs to be modified by using surfactant or other chemicals to obtain a uniform dispersion of nanocellulose in the matrix [64].

In melt mixing/compounding, nanocellulose is dispersed into the melted polymer matrix. The solution is then extruded to obtain nanocomposites [63]. Commonly, extrusion temperature is limited to about 200°C because nanocellulose has a glass transition temperature of around 200-230°C and decomposition starts at 260°C [64]. Uniform dispersion and distribution of nanocellulose in the matrix as well as strong interaction between nanocellulose and matrix are very important factors to improve the properties of nanocomposites. Melt mixing is usually applied for non-polar polymer matrix, thus surface modification of nanocellulose needs to be conducted to obtain uniform dispersion of nanocellulose in the matrix [25].

Several researchers have produced cellulose-based nanocomposites. In 2017, Fahma and the team [65] produced PVA nanocomposite films reinforced with CNF isolated from OPEFBs by studying the effect of sonication time on the morphology and properties of produced nanocomposites. The nanocomposite films were produced by the solution casting method. The result showed that by increasing the sonication time by up to 9 min, the mechanical properties of nanocomposite films increased. Another study was conducted by Robles et al. [66] that produced a PLA nanocomposite reinforced with surface-modified CNF and CNC isolated from blue agave bagasse. CNF was modified using 3-aminopropyl triethoxysilane, while CNC was modified using dodecanoyl chloride. The result showed that the addition of nanocellulose increased the interaction between matrix and fillers. In addition, the crystallization and thermal properties of produced nanocomposites were also improved.

PVA–Banana fiber composite films were prepared by solution casting method with different content of nanocellulose from microcrystalline cellulose (MCC). The nanocellulose addition to PVA–banana pseudostem fiber composite films significantly improve their mechanical and water barrier properties making them a suitable alternative to plastic packaging films [67]. Meanwhile, Lisdayana et al. studied the effect of nanocellulose addition and three types of starch (corn starch, cassava starch, or sago starch) on the mechanical properties of thermoplastic starch (TPS)–PVA–cellulose nanocomposite films. The difference of amylose content in the different starch influenced the properties of produced nanocomposite films [68].

Due to the promising properties as reinforcing material, nanocellulose can be used for processing various bionanocomposites such as coating, foams, films, etc [69]. The application of these nanocomposites covers many applications including automotive industry which can be found in internal parts of the car such as door panels, trim parts in dashboards, spare tire covers, etc. Such applications have been used in several commercial products [70]. Mitsubishi motors have employed poly(butylene succinate) reinforced with bamboo fibers for interior components, and Toyota has used different polymer composites reinforced with natural fiber as spare tire covers in the RAUM 2003 model [71].

6. Nanocellulose for biomedical application

Nanocellulose applications have been widely used in the biomedical field, where they are used either as single components or in composites with other materials. Owing to its excellent physical properties, biocompatibility, biodegradability, and low toxicity makes them a suitable candidate in biomedical applications. The terms biocompatible means that the material can be implanted in the body without giving any negative effects. While biodegradable means that the materials can be broken down or degraded. In a previous review article, cellulose was considered as slowly degradable or non-biodegradable in vivo, because it lacks the cellulase enzyme [72].
Plant-based nanocellulose, such as CNF and CNC contain lignin and hemicellulose which makes them less likely to be applied in biomedical field. Besides, they need several chemical treatments to remove lignin and hemicellulose contents, which might cause deleterious effects due to the remaining chemicals and their by-products [32]. Compared to CNF and CNC, BNC is generally considered to be safer for application in biomedical field. This is because BNC is free from lignin and hemicellulose contents, doesn’t need any chemical treatments, and doesn’t contain any sulphur [32,73].

Although some researchers reported that nanocellulose is low or nontoxic, when applying it in the biomedical field, the issues of toxicity and safety have not revealed its potential risk to human health and the environment either [74].

The study conducted by Kovacs et al. [75] about the ecotoxicology of CNC with rainbow trout hepatocytes and nine aquatic species revealed that CNC had low environmental risk and toxicity. In an article, it was also reported that CNC is non-cytotoxic, non-immunogenic, and a good candidate for tissue culture medium to assist cell proliferation [76]. In fact, the intracellular toxic effect and inflammatory response of CNC were much lower than that of using multiwalled carbon nanotubes and crocidolite fibers [77]. Research on the health effects of microfibrillated cellulose (MFC) on mouse macrophages and human monocyte derived macrophages were also studied by Vartiainen et al. [78]. The result showed that the produced MFC is not cytotoxic and doesn’t cause any inflammation effects in the macrophages.

According to a previous article by Naz et al. [18], nanocellulose, especially bacterial nanocellulose, can be applied in various biomedical fields, including skin therapy, artificial blood vessels (cardiovascular implants), cartilage meniscus implants, tissue engineering, bone tissue implants, neural implants, wound dressing, artificial cornea, urinary conduits, dental implants, drug delivery applications, etc. In tissue engineering applications, nanocellulose can be produced as scaffolding materials which provide a good environment for cells and stimulates cell attachment and proliferation [72].

The most important characteristic for wound dressing materials is the ability of the materials to absorb and remove exudate from a wound surface during the dressing process and after recovery, respectively. Hakkarainen et al. [79] studied the use of nanofibrillated cellulose isolated from the bleached birch pulps as wound dressing materials. The result showed a good biocompatibility between the isolated nanofibrillated cellulose and the skin graft donor sites. In addition, the isolated nanofibrillated cellulose adheres well with the wound and is easily detached by itself after skin recovery.

In drug delivery application, there are three common types of nanocellulose-based drug deliveries, including micro-spheres/particles, hydrogels, and membranes or films [72]. The application of nanocellulose, especially CNC in drug delivery purpose was studied by Lin et al. [80]. They produced pH-sensitive CNC/sodium alginate microsphere. The result showed that the incorporation of CNC resulted in more consistent swelling patterns, a more efficient encapsulation process, and improved drug load and release profiles.

7. Nanocellulose for food packaging application

A good packaging material is that which can maintain the quality of the products and protect them against any chemical, physical, or biological deterioration. Hence, the packaging material should have a good barrier against oxygen, water vapor, grease, and microorganisms [11,81]. Due to their excellent gas and water barrier, synthetic polymers derived from petroleum based materials are generally used as packaging materials. However, due to the concerns about the environmental impact on using nonrenewable resources, the use of renewable resources is now more preferred [82].

From this point on, industry and academia continue to work on developing bio-based and degradable polymer packaging alternatives with more competitive features. Several researchers have reported that the use of bio-based and degradable polymers can reduce the environmental effect of petroleum based materials. Bio-based polymers mean that the polymers are derived from renewable resources that might be non-biodegradable. Meanwhile, biodegradable polymers can be derived either from renewable or fossil fuels which are degradable. The combination characteristics of renewable and biodegradable materials are more preferred for packaging applications [8].

Cellulose, starch, agar, chitosan, gelatin, collagen, etc. are examples of naturally occurring biopolymers. Apart from naturally occurring biopolymers, the use of synthetic biopolymers, such as polylactic acid (PLA) and polyvinyl alcohol (PVA) have also been studied. A previous review article reported that the use of synthetic biopolymers provides many excellent properties, such as flexibility, durability, a higher gloss, clarity, and better mechanical properties [83,84]. Even though the use of biopolymers can successfully answer the problems regarding cost, sustainability, energy consumption, and environmental
impact, they showed poorer mechanical, thermal, and barrier properties compared to petroleum-based materials. Hence, for a more successful application, biopolymers are reinforced with nanomaterials, such as nanocellulose [84,85].

The expansion of nanocellulose applications is mostly directed to the development of green packaging. This can be seen from the increasing number of scientists researching the characteristics and developing functionalities features of nanocellulose in food packaging. The incorporation of nanocellulose into polymer matrix for the production of biodegradable packaging materials has been reported by several researchers. Nanocellulose as reinforcing agent in polymer composite packaging was demonstrated by Fahma et al [86] through producing thermoplastic starch (TPS)-PVA composite films reinforced with cellulose nanofibers isolated from OPEFBs. The films were prepared by the casting method and glycerol was added as the plasticizer. The results showed that the incorporation of 5wt% CNF into TPS-PVA composite films without glycerol resulted in an increase of the films’ tensile strength by up to 28% from 48.30 MPa to 61.76 MPa. The crystallinity of the films was also increased with the increase of nanocellulose content. Meanwhile, their elongation at break and water vapor transmission rates were decreased.

Sanchez-Garcia and Lagaron [87] produced PLA composites reinforced with cellulose nanowhiskers (CNW) by the solution casting method. CNWs were dispersed in PLA matrix by two methods: freeze-dried CNW, and solvent-exchanged CNW with chloroform. The results showed that the addition of 3 wt% CNW into the PLA matrix resulted in a decrease of water and oxygen permeability by up to 82% and 90%, respectively. Curiously, the addition of CNW decreased the tensile strength and tensile modulus of the composites compared to neat PLA, while increasing their elongation at break.

Apart from being a reinforcing agent, nanocellulose can also reduce the permeability of oxygen and water vapor in the packaging [88]. Oxygen barrier property increased to 47.3% with an increase in CNF of 0.25, 0.50, and 1 wt% in CNF/PLA films [89]. Nanocellulose has good water vapor barrier properties, due to its size, and the rigid network in the packaging matrix results in swelling limitation [90]. Paper packaging coated with a modified 1% NCF formulation added to PLA resulted in the lowest WVTR value of 34g/m2/day. The value obtained is much lower than the control [91].

Several surface modifications of nanocellulose were carried out to produce or improve the functional properties of the packaging material. Modifications on the surface of nanocellulose can increase the hydrophobicity of packaging materials [92,93]. (TEMPO)-oxidized cellulose nanofibril (TOCN) films crosslinked with metal ions can improve the water resistance properties [94].

In addition, the design of active packaging or smart packaging also involves nanocellulose as a carrier for several bioactive compounds, such as antioxidants, antimicrobials and antifungals in the packaging matrix [95-97]. There have been reports on nanocellulose utilization in packaging applications including intelligent packaging, ultra-violet screening packaging, see-through packaging, and anti-microbial packaging [69]. Nanocellulose is emerging as a renewable green material that has the potential to be used as fillers and reinforcement composite, coatings, surface modifications, carriers of bioactive compounds, and many more uses for packaging industrial applications.

**8. Conclusions**

The exceptional properties of nanocellulose, such as being lightweight, having better mechanical, thermal, and barrier properties, biodegradability, biocompatibility, etc. have made a contribution to the development of nanotechnology. With the advance of nanotechnology, nanocellulose has been used as a reinforcement in composites production, which is known as nanocomposites. The use of nanocellulose as a reinforcing agent/nanofiller could replace the use of synthetic fillers, which are usually produced from non-renewable resources. However, certain surface modification is needed when mixing nanocellulose with non-polar polymers. Nanocellulose can be applied not only in the composite field, but also in the biomedical and food packaging fields. Due to its biocompatibility, biodegradability, good barrier properties, and nontoxicity, nanocellulose is a good candidate for biomedical application. Several researches regarding the potential application of nanocellulose in composites, biomedical, and food packaging fields have been discussed in this paper. Even though several researchers have reported the potential application of nanocellulose in the biomedical field, further research regarding the toxicity of nanocellulose needs to be investigated.

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